Generally Recognized as Safe (GRAS) Notice for Dried L-Tryptophan Fermentation Product as a Source of Tryptophan in Swine Feed

Prepared for:
U.S. Food and Drug Administration
Center for Veterinary Medicine
Division of Animal Feeds

Prepared by:
CheilJedang Corporation

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PART 1 GRAS Notice

CJ CheilJedang Corporation (hereinafter referred to as 'CJ') is submitting a GRAS notice for the substance Dried L-Tryptophan Fermentation Product as a source of L-tryptophan in swine diet.

1.1 Name and Address of Organization

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1.2 Name of the Notified Substance

The common or usual name of the subject substance of this notification is 'Dried L-Tryptophan Fermentation Product' which is a source of the essential nutrient L-tryptophan. The level of L-tryptophan in this substance is a minimum of 60%. Dried L-Tryptophan Fermentation Product also contains biomass originated from fermentation broth of *Corynebacterium glutamicum*. The trade name of the product is 'TRP Pro'.

1.3 Intended Conditions of Use

Dried L-Tryptophan Fermentation Product is to be used as an ingredient in swine feed according to current good manufacturing and feeding practice as defined in 21 CFR §582.1 (b) ('Substances that are generally recognized as safe'). L-Tryptophan is an essential amino acid that is typically considered to be the fourth amino acid for livestock. L-Tryptophan will be incorporated into the diet at levels commensurate with the nutritional requirement. Therefore, the required level will be decided on a case-by-case basis by animal nutritionists, based on good feeding practice for the target species.

1.4 Statutory Basis for GRAS Determination

This GRAS conclusion is based on the scientific procedures as provided in 21 CFR §570.30 (a) and (b).

1.5 Federal Food, Drug, and Cosmetic Act Premarket Approval Exemption

The submitter has determined that the use of Dried L-Tryptophan Fermentation Product as produced by fermentation with *Corynebacterium glutamicum*, for use as a nutrient (L-tryptophan) in swine feed is Generally Recognized as Safe (GRAS) based on scientific procedure and is thus exempt from the premarket approval requirement of the Federal Food, Drug and Cosmetic Act (21 U.S.C §301 et seq.).

1.6 Availability of Information for FDA Review

CJ agrees to make the data and information pertaining to this submission available to FDA.

CJ agrees to both of the following procedures for making the data and information available to FDA:

(A) Upon FDA's request, CJ will allow FDA to review and copy the data and information during customary business hours at the address specified for where these data and information will be available to FDA; and
(B) Upon FDA's request, CJ will provide FDA with a complete copy of the data and information either in an electronic format that is accessible for FDA evaluation or on paper.

1.7 Freedom of Information Act 5 U.S.C 552 Disclosure Exemption

CJ has placed proprietary and confidential information in five appendices: Appendix 1, 'Compositional Analysis (CONFIDENTIAL)'; Appendix 2, 'Pre-Fermentation Information (CONFIDENTIAL)'; Appendix 3, 'Manufacturing Process (CONFIDENTIAL)'; 'Appendix 9, Non-tryptophan Components Assessment and Validation (CONFIDENTIAL)'; and 'Appendix 10, Biogenic Amines Assessment and Validation (CONFIDENTIAL)'.

1.8 Certification of Complete, Representative Submission

To the best of our knowledge and belief, this GRAS notice is a complete, representative and balanced submission that includes unfavorable information, as well as favorable information, known to CJ and pertinent to the evaluation of the safety and GRAS status of the use of Dried L-Tryptophan Fermentation Product produced by fermentation with genetically engineered *Corynebacterium glutamicum* as a source of L-tryptophan for swine feed.

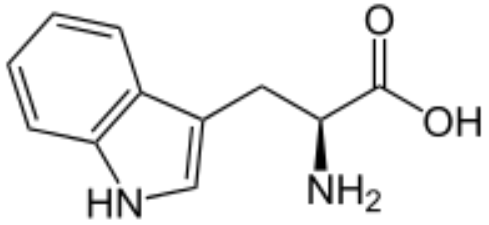
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Aleksandar Todorovich
Regulatory Affairs Manager

PART 2 GRAS Notice: Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

2.1 Scientific Data and Information that Identifies the Notified Substance

2.1.1 Name and Other Identities

Chemical name according to IUPAC nomenclature	(2S)-2-amino-3-(1H-indol-3-yl)propanoic acid
Synonyms	L-Tryptophan; L-α-Amino-3-indolepropionic acid; (S)-2-Amino-3-(3-indolyl)propionic acid
CAS No.	73-22-3
EC No.	200-795-6
Appearance	Pale brown or brownish free-flowing granules
Molecular mass	204.23 g/mol
Molecular formula	$C_{11}H_{12}N_2O_2$
Structural formula	

This GRAS notice covers Dried L-Tryptophan Fermentation Product produced by fermentation with *Corynebacterium glutamicum*, with a minimum purity of 60% of L-tryptophan. L-Tryptophan is the active substance in the Dried L-Tryptophan Fermentation Product. Due to its dedicated chemical properties, L-tryptophan can only be found as free amino acid, which must not be transformed into a salt to be stable during the production, storage and application.

2.1.2 Composition

The majority of Dried L-Tryptophan Fermentation Product is L-tryptophan (≥ 60%). The product also contains other amino acids, sugars, crude ash, crude fat, moisture, and nucleic acids. As shown in Table 2.1, the analysis of the five batches of Dried L-Tryptophan Fermentation Product demonstrates that the finished product is reproducibly manufactured. Additional information regarding the analytical assessment of the product composition is referred to Appendix 1.

Table 2.1. Chemical composition of Dried L-Tryptophan Fermentation Product (Appendix 1)

Parameter (%)	(b) (4)	Average
Moisture		1.5
Crude ash		7.8
Crude protein (N x 6.25)		68.3
Crude fat B (with HCl)		3.4
Starch		< 0.2
Total sugars calc. as sucrose		4.8
Crude fiber		< 0.5
Tryptophan		62.8
Total nucleic acids		0.64
Nucleosides		0.13
DNA		0.35
RNA		0.16
Other amino acids		13.48
Lysine		0.87
Methionine		0.28
Cystine		0.12
Threonine		0.82
Serine		0.65
Glutamic acid		2.65
Proline		0.59
Glycine		0.84
Alanine		1.60
Valine		1.00
Isoleucine		0.78
Leucine		1.29
Tyrosine		0.48
Phenylalanine		0.63
Arginine		0.90
Chloride		0.13
Calcium		1.52
Phosphorus		0.47
Sodium		0.51
Potassium		0.85
Sulphur		1.31

* All batch products used in this analysis are pilot products.
** All analytical results are as-is basis.

2.1.3 Fermentation Organism

The fermentation microorganism is a genetically modified strain of *Corynebacterium glutamicum* KCCM 80346 (*C. glutamicum* KCCM 80346). The genetic modification method and characterization of the production strain can be found in Appendix 2. The safety of the production microorganism can be found in Section 6 of this dossier, Appendix 2 and Appendix 11.

2.2 Manufacturing Process

Dried L-Tryptophan Fermentation Product is produced by fermentation with *C. glutamicum* KCCM 80346 as a production strain. After fermentation, the fermentation broth is transferred to the inactivated broth tank through a plate heat changer to sterilize the broth and adjust pH with (b) (4) . Detailed information of manufacturing process is provided in Appendix 3.

Raw materials used for producing Dried L-Tryptophan Fermentation Product are feed grade specifications which are suitable for use in the manufacture of swine feed (Appendix 3). Dried L-Tryptophan Fermentation Product is manufactured in accordance with good manufacturing practices as set forth in 21 CFR §507 and meets the requirements of the US Food Safety Modernization Act (FSMA). As part of the facility's FSMA compliance, a Hazard Analysis Risk-Based Preventive Control plan has been implemented and conducted to evaluate the facility, raw materials, processes and product for potential physical, chemical and biological hazards. In order to mitigate potential risks, a hazard analysis was conducted that includes a risk assessment of the raw materials and processing steps with the implementation of appropriate preventive controls to ensure the safety of the product. These control measures are in place to effectively eliminate or reduce hazards to acceptable levels. The facility also uses prerequisite programs such as an approved supplier program to ensure the safety of the raw materials and that the raw materials are appropriate for their intended use and for the manufacture of a feed ingredient. Material suppliers are initially and periodically qualified and verification activities are performed commensurate to the risk of the material. The applicant also declares that no antimicrobial compounds (including antibiotics) were used in the production process.

2.2.1 Ingredient Stability (Shelf-life)

The stability of Dried L-Tryptophan Fermentation Product was observed by measuring the contents of L-tryptophan and moisture under the general storage conditions (b) (4) The content of L-tryptophan and moisture were analyzed in real-time for 12 months.

As shown in Table 2.2, none of the tested samples showed a significant decrease in the level of the L-tryptophan at the tested time points. The specified content of L-tryptophan (minimum 60%) was maintained in all samples over the tested periods. The full stability report is provided in Appendix 4.

Table 2.2. Shelf-life of Dried L-Tryptophan Fermentation Product

Batch	Parameter	Storage time (month)				
		0	3	6	9	12
DWFP210930	L-Tryptophan (%)*	(b) (4)				
DWFP211005	L-Tryptophan (%)*					
DWFP211007	L-Tryptophan (%)*					

* Dry matter basis

L-tryptophan was stable over the 12 months of testing, and it demonstrated the product stability throughout the testing period at ambient temperatures.

2.2.2 Stability upon Addition to Animal Feed

A 3-month stability test with mash feed similar to commercial swine feed was conducted to demonstrate the stability of Dried L-Tryptophan Fermentation Product when mixed in a complete feed. The added amount of L-tryptophan is 0.508%. The content of free L-tryptophan was analyzed in real-time for 3 months. Free L-Tryptophan represents added L-tryptophan from Dried L-Tryptophan Fermentation Product.

As shown in Table 2.3, none of the tested samples showed a significant decrease in the level of the L-tryptophan at the tested time points. The specified content of free L-tryptophan was maintained in all samples over the tested periods. The full study report can be found in Appendix 5.

Table 2.3. Stability of Dried L-Tryptophan Fermentation Product in mash feed

Batch	Parameter	Storage time (month)			
		0	1	2	3
		Formulated level of L-Tryptophan Fermentation Product 0.83% (0.508% of added L-tryptophan)			
Mash feed with DWFP210930	L-Tryptophan (%)	(b) (4)			
Mash feed with DWFP211005	L-Tryptophan (%)				
Mash feed with DWFP211007	L-Tryptophan (%)				

* Analysis value minus the determined blank value of the feed (0.026% L-tryptophan)

This study demonstrated that Dried L-Tryptophan Fermentation Product is a stable source of L-tryptophan when added to complete mixed feed over a 3-month period.

2.3 Specifications

The specification of Dried L-Tryptophan Fermentation Product is established based on the assay of 5-batch product. The analytical data supporting the specifications is reported in Table 2.1 and Appendix 1. The product specifications are provided in Table 2.4.

Table 2.4. Specification of Dried L-Tryptophan Fermentation Product

Parameter	Specification
L-Tryptophan (%, dry matter basis)	≥ 60
Moisture (%)	≤ 5
Ash (%)	≤ 10

The hazardous substances, heavy metals, in Dried L-Tryptophan Fermentation Product was analyzed. Certificate of analysis is provided in Appendix 6. As shown in Table 2.5, the low concentration of heavy metals, lead, mercury, and arsenic, were detected. The level of cadmium and mercury in the Dried L-Tryptophan Fermentation Product is below the limit of detection. Hence there is no concern about the safety due to heavy metals in the animal and human, based on the NRC established tolerances (NRC, 2005).

Table 2.5. Heavy metals in Dried L-Tryptophan Fermentation Product

Parameter	Batch		
			(b) (4)
Lead (mg/kg)	0.028	0.025	0.023
Cadmium (mg/kg)	< 0.010	< 0.010	< 0.010
Mercury (mg/kg)	< 0.010	< 0.010	< 0.010
Arsenic (mg/kg)	0.15	0.15	0.14

* Cadmium levels represented in this table were expressed with the different dilution factors. (Cadmium LOQ (ng/kg) = 5.664)

2.4 Intended Use (Utility) of Dried L-Tryptophan Fermentation Product

Dried L-Tryptophan Fermentation Product is to be used as L-tryptophan supplemental nutrient in swine feed in accordance with good manufacturing or feeding practice as defined in 21 CFR §582.1 (b) ('Substances that are generally recognized as safe'). L-tryptophan is an essential amino acid in all animal species (EFSA, 2015). The level of supplementation varies between species and depends on the nutritional content of the diet (specifically the amino acids content). Therefore, the use of supplementation will be determined on a case-by-case basis by animal nutritionists, based on good feeding practice.

L-tryptophan is usually the fourth and third limiting amino acid for swine and poultry, respectively (Duttlinger et al, 2007 and Fouad et al, 2021). Like L-lysine and L-threonine, L-tryptophan is an indispensable amino acid for body protein deposition, growth, and maintaining animal health. Thus, a

dietary deficiency in L-tryptophan affects the utilization of previous dietary limiting amino acids and consequently animal growth and health status. In addition to its effect on protein synthesis, L-tryptophan plays a specific role in other physiological processes. For example, being a precursor of niacin or of the neurotransmitter serotonin which is involved in feed intake regulation (Chen et at, 1996). Like other amino acids, L-tryptophan is a naturally occurring constituent of the metabolism in humans and all mammalian species, birds, fish, and most other species.

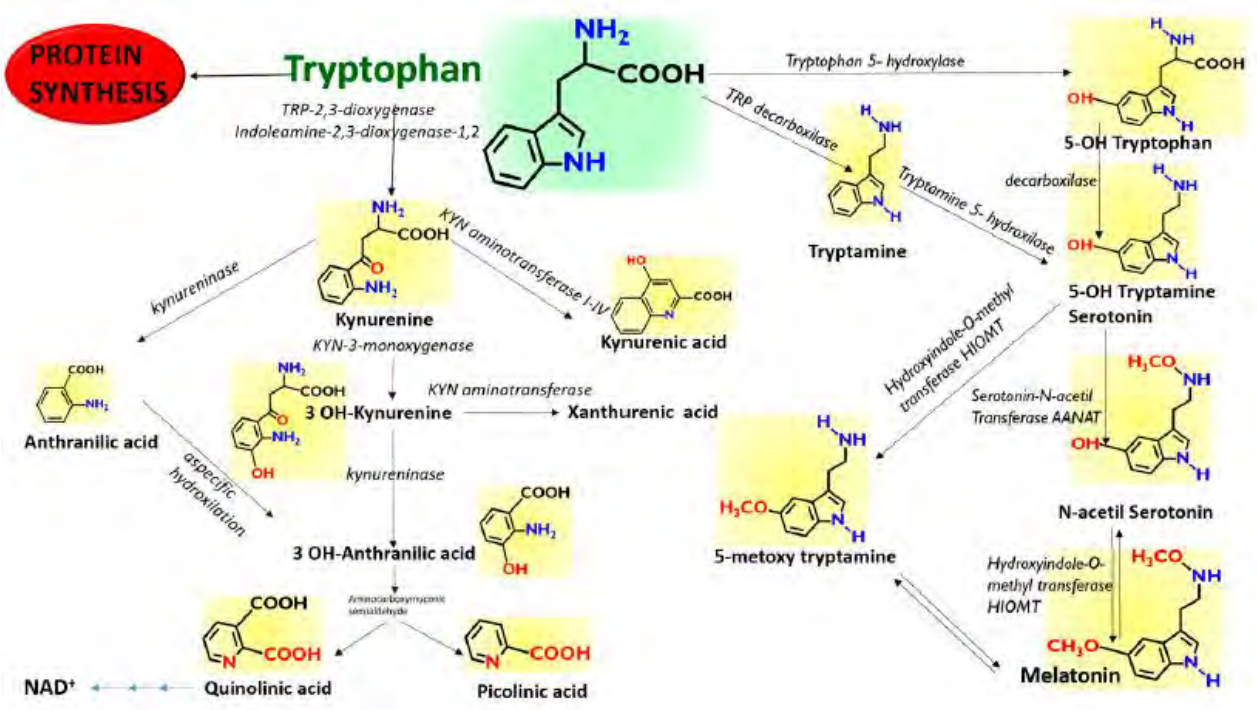


Figure 2.1. L-tryptophan pathways (Vitalini et al., 2020)

Dried L-Tryptophan Fermentation Product can be added directly to the feeding stuffs/complementary feeding stuffs or via premixes. No inclusion levels are proposed as the requirements in quantitative terms as it is dependent on the species, the physiological state of the animal, the performance level and the environmental conditions, as well as the amino acid composition of the non-supplemented diet. The formulator of the feed will determine the required level of amino acid supplementation.

Dried L-Tryptophan Fermentation Product is the subject of this application. The active substance is L-tryptophan. Any component of Dried L-Tryptophan Fermentation Product does not differ significantly from the constituents of the ordinary diet of target swine species.

The biomass portion (*C. glutamicum* KCCM 80346) of Dried L-Tryptophan Fermentation Product is dried and inactivated. This is derived from the same wild-type strain (*C. glutamicum*) used in the Dried L-Lysine Fermentation Product (AAFCO, 2018). According to the AAFCO Official Publication (AAFCO, 2018), Dried L-Lysine Fermentation product has been shown to be effectively used as an

alternative to L-lysine monohydrochloride (L-lysine without biomass product) as a supplemental L-lysine source in swine and poultry diets. The biomass has been demonstrated to not interfere with the L-lysine availability. This has been confirmed comparing the bioavailability of L-lysine and L-lysine sulfate (Lysine Fermentation Product, Htoo et al., 2016) and L-valine (98%) and spray dried L-valine with fermentation biomass (Oliveira et al., 2019) in weanling pigs.

A recent publication examined the bioavailability of three amino acids: L-threonine (> 75%), L-valine (> 70%) and L-tryptophan (> 60%) fed to either broiler chicks or weanling pigs with their respective dried fermentative biomasses produced by CJ (Wensley et al., 2020). It was concluded that the respective amino acids, L-threonine, L-valine and L-tryptophan, when formulated on an equal amino acid basis were bioequivalent to commercially available forms of the amino acids by comparison with growth parameters (ADG and FCR). Dried L-Tryptophan Fermentation Product, the substance of this dossier, was one of the amino acids used in this study. This data clearly demonstrates that there is no expectation that the biomass will negatively impact the bioavailability of tryptophan from the Dried L-Tryptophan Fermentation Product.

Wensley et al. (2020) publication included a 21-day swine utility trial conducted by Kansas State University to specifically compare CJ's Dried L-Tryptophan Fermentation Product to commercially available L-tryptophan (98%). The trial utilized 315 barrows initially averaging 11.3 kilograms. Pigs were weighed place into pens (5 pigs/pen), pens blocked on weight and assigned to one of four dietary treatments (15 or 16 replicates/treatment). Experimental treatments were: Positive Control (PC) containing a 21% SID tryptophan to lysine ratio using commercially available feed grade L-tryptophan (98%), a Negative Control (NC) with 16% SID tryptophan to lysine ratio (no supplemental L-tryptophan added) or NC with Dried L-Tryptophan Fermentation product added at 0.104% to equal the SID tryptophan to lysine ratio (21%) of the PC diet or NC with Dried L-Tryptophan Fermentation Product added at 150% (0.156%) providing a tryptophan to lysine ratio of 23.5%. Growth data was analyzed as a randomized complete block design using PROC GLIMMIX of SAS with the pen used as the experimental unit.

Table 2.6. Bioavailability results of Dried L-Tryptophan Fermentation Product compared to positive and negative control diets as demonstrated by growth (Wensley et al., 2020)

Criteria	Positive control (PC)	Negative control (NC)	NC with Dried L-Tryptophan Fermentation Product 21% SID[1] Trp:Lys	NC with Dried L-Tryptophan Fermentation Product 23.5% SID[1] Trp:Lys	SEM	*p*-value
Body weight, kg						
Day 0	11.3	11.3	11.2	11.3	0.25	0.723
Day 21	23.5[a]	22.8[b]	23.5[ab]	23.0[ab]	0.37	0.019
Feed intake, g						
Day 0 - 21	865	836	854	833	18.0	0.132
Average daily gain, g						

Criteria	Positive control (PC)	Negative control (NC)	NC with Dried L-Tryptophan Fermentation Product 21% SID[1] Trp:Lys	NC with Dried L-Tryptophan Fermentation Product 23.5% SID[1] Trp:Lys	SEM	*p*-value
Day 0 - 21	576[a]	549[b]	580[a]	556[ab]	8.9	0.004
Gain to feed ratio						
Day 0 - 21	0.667[ab]	0.658[b]	0.680[a]	0.668[ab]	0.0077	0.045

[1] Standardized ileal digestible.
[a-b] Values with different superscripts differ, $p < 0.05$.

Pigs fed NC diet (no supplemental L-tryptophan, SID Trp:Lys = 16%) had reduced (P < 0.05) body weight and daily weight gain compare to PC-fed pigs. Increasing the digestible L-tryptophan level with Dried L-Tryptophan Fermentation Product in the NC diet to an equal level as the PC diet, increased (P < 0.05) body weight, daily weight gain and improved (P < 0.05) gain to feed ratio compared to the NC diet. All performance parameters measured were similar (P > 0.10) to the PC-fed pigs. Gain to feed ratio of pigs fed the Dried L-Tryptophan Fermentation Product fed the equivalent level of tryptophan as the PC diet actually had a numerically higher gain to feed conversion ratio compared to the PC; which may be associated with the additional nutrients contributed by the biomass. Increasing the amount of Dried L-Tryptophan Fermentation Product to 150% (23.5% SID tryptophan to lysine ratio) of the level of L-tryptophan in the PC diet did not have any negative (P > 0.10) impacts on pig performance. This study confirms the L-tryptophan from Dried L-Tryptophan Fermentation Product is bioavailable to target species. In conclusion, Dried L-Tryptophan Fermentation Product appears to be a suitable alternative to crystalline L-tryptophan in nursery pig diets as there was no difference in performance when pigs were fed the same SID Tryptophan to Lysine levels from either source.

This study was conducted to demonstrate that the limited biomass in the GRAS substance does not impact the L-tryptophan bioavailability. The model chosen (weanling pigs) has been demonstrated to be an effective model to discern the limitation of nutrient availability.

The intent of demonstrating bioavailability of essential nutrients is to provide a clear demonstration that the manufacture of the essential nutrient and its composition does not impact the bioavailability of the essential nutrient to the animal. Some have expressed a concern that biomass when left in the fermentation derived manufacture of essential nutrients may impact the overall bioavailability. Because of this issue, CJ provided an in vivo test to demonstrate that the limited biomass in the GRAS substance did not impact the bioavailability. The model chosen (growing swine) has been demonstrated to be an effective means to discern if there is a factor that will limit the availability of the nutrient.

In their review, Kong and Adeola (2014) stated that bioavailability studies (which cover digestion, absorption, and utilization) is considered the absolute standard for estimating bioavailable amino acid compared to other methods. CJ completed and published a 28-day study using weanling pigs as a model (Wensley et.al, 2020). The study demonstrates that there was no impact of the biomass (27%) on

bioavailability of the L-tryptophan content of the GRAS substance. This model would suggest that the *C. glutamicum* biomass would not impact the bioavailability of L-tryptophan. This was confirmed by the study conducted in swine (Oliveira et al., 2019) with a L-valine fermentation product containing approximately 35% biomass. Also, Carl Parsons (1996) review of digestible amino acids in poultry and swine found, generally a good correlation when using either cecetomized roosters or ileal-cannulated swine; however, as Kong and Adeola noted digestibility is only one factor when assessing bioavailability. As pointed out earlier, other *C. glutamicum* amino acids sources (lysine, threonine and valine) have been assessed for bioavailability, and as suggested in AAFCO definition 36.15, there is no concern of this source of amino acids for use in livestock, poultry and aquaculture. When feeding ruminants amino acids, the bacteria rich rumen typically consumes the amino acids and building microbial proteins that are digested and absorbed later down the gastrointestinal tract.

The data presented positively demonstrates that Dried L-Tryptophan Fermentation Product is a bioavailable source of L-tryptophan for the intended use in swine feed.

Part 3 GRAS Notice: Target Animal and Human Exposures

3.1 Target Animal Exposure

L-tryptophan is an essential amino acid in all animal species (EFSA, 2015), including livestock (NRC, 2012). The level of supplementation is dependent on the nutritional content of the diet (specifically the amino acids content). Therefore, the use of supplementation will be determined on a case-by-case basis by animal nutritionists, based on good feeding practice.

Based on the overall level of supplementation in the most fortified diets, the maximum level of L-tryptophan would, in normal feeding practices, be approximately from 0.11% to 0.22% of the swine feed (0.18% to 0.37 % Dried L-Tryptophan Fermentation Product) (NRC, 2012). Therefore, the usage level of Dried L-Tryptophan Fermentation Product in the formulated feed will be depends on the L-tryptophan naturally occurring content in the feed, a maximum usage would be considered 0.37% of the feed.

The majority of the non-L-tryptophan components (Table 6.1) of Dried L-Tryptophan Fermentation Product are either essential nutrients or typical components of swine feed (amino acids, minerals and organic acids) and are consistent with normal components of feed, as such would not be a source of residues beyond that found in traditional livestock feeds.

3.2 Human Food Exposure

L-tryptophan is a required nutrient for human, since the occurrence of L-tryptophan in proteins is generally less than other amino acids and because it is a precursor for important metabolites such as serotonin and nicotinamide, in the latter case giving it vitamin-like properties through its ability to replace dietary niacin.

Dried L-Tryptophan Fermentation Product is intended for use in swine feed only as a nutritional source of the essential amino acid, L-tryptophan. The other components of the substance are nutrients and are available for uptake, metabolism and growth. Therefore, the composition of the meat products from animals fed Dried L-Tryptophan Fermentation Product, should be no different than from animals fed a nutritionally complete diet.

Also, in general, amino acids cannot be stored by the organism. Free amino acids, whether ingested in commercial synthetic form or released after the digestion of proteins by proteolytic enzymes, are absorbed through the intestinal mucosa to enter the blood stream. After absorption, alpha amino acids are directly used in protein synthesis or rapidly metabolized into intermediates in the citric cycle as evidenced by the presence of only trace amounts of alpha amino acids in the plasma.

Thus, it can be concluded that there will be no additional exposure to L-tryptophan above the natural basal content for the consumer raised by digested meat produced from animals fed with compounded feed supplemented by Dried L-Tryptophan Fermentation Product.

Part 4 GRAS Notice: Self-Limiting Levels of Use

There is no self-limiting use information specific to this substance.

Part 5 GRAS Notice: Experience Based on Common Use in Food Before 1958

The GRAS determination is not based on common use in animal feed prior to 1958.

Part 6 GRAS Notice: Narrative

6.1 Safety of *Corynebacterium glutamicum* – Production Organism

Corynebacterium glutamicum (*C. glutamicum*) is a gram-positive bacterium belonging to the family of Corynebacteriaceae. This strain is scientifically recognized as safe and provides no negative impact on human and the environment. Additionally, this strain has a long history of safe use in industrial production (Eggeling and Bott, 2005). In addition, *C. glutamicum* is a GRAS microorganism and has a 'Qualified Presumption as Safe' (QPS) status (EFSA, 2011). A description and summary of the QPS review of *C. glutamicum* is provided in Appendix 11.

C. glutamicum is an authorized source for a number of feed ingredients. It is listed as a feed ingredient in the AAFCO OP (AAFCO, 2018). It is a source organism for Condensed Extracted Glutamic Acid Fermentation Product and Dried L-lysine Fermentation Product as well as Liquid L-lysine Fermentation Product (AAFCO, 2018. 36.1; AAFCO, 2018. 36.16 and AAFCO, 2018. 36.17). In 2014, the US Food and Drug Administration, Division of Animal Feeds (OS&C/FDA) had reviewed the safety assessment of this source organism for the use in animal feed. Based on that recent review, CJ extensively reviewed the recent literature since 2003 (Appendix 11). Overall, no studies were retrieved either in the electronic literature search (ELS) or follow-up selective searches that contained information indicating potential safety issues or hazards associated with *C. glutamicum*. This is consistent with the previous safety assessment completed by the US FDA, Division of Animal Feeds.

In addition, Dried L-Threonine Fermentation Product (≥ 75% L-threonine) produced by bioengineered *Corynebacterium glutamicum* KCCM 80178 and was submitted as animal GRAS notice (AGRN 34). This notice was reviewed and a no question letter was issued (August 13, 2020). The Dried L-Threonine Fermentation Product is now listed in Chapter 6, section 101 of the AAFCO Official publication as an authorized feed ingredient.

6.2 Safety Considerations due to the Nature of Modification to *Corynebacterium glutamicum*

The production microorganism used to produce Dried L-Tryptophan Fermentation Product is a genetically modified strain of *C. glutamicum.* The details of the genetically modified strain of *C. glutamicum* are provided in Appendix 2. The assessment of the genetic engineering process demonstrates that there is no hazard imparted due to the engineering process. This data is summarized in the sections below.

Dried L-Tryptophan Fermentation Product is intended for use as a nutrient for animal consumption. Generally, a GRAS notice addresses the potential human dietary consumption of a component of animal

feed due to consumption of animal products and tissues in which the component may be present. In this case, however, there is no need to determine the estimated daily intake (EDI) of the Dried L-Tryptophan Fermentation Product for human consumption. The Dried L-Tryptophan Fermentation Product and any of the described biomass (see above) will be metabolized when the animal consumes and digests its feed (like all feed). Dried L-Tryptophan Fermentation Product derived from the genetically modified *C. glutamicum* will be indistinguishable from other sources, as will be the potential non L-tryptophan components, which are all normal components of animal feed.

1) Information on any toxic, allergenic or other harmful effects on human or animal health

The genetic modifications made, resulting in strain *C. glutamicum* KCCM 80346, exclusively correspond to the overexpression or elimination of several enzymes in its metabolism. It has been used for the manufacturing of feed additives for many years and is generally accepted as safe. The open reading frames (ORFs) of production strain were analyzed to assess the absence of shifting open reading frames which does not associated with intended genetic changes and potential of spill-over effects. Any safety concerns were not observed based on this analysis (Appendix 2).

The pathogenicity-related genes were identified using the whole genome sequence of *C. glutamicum* KCCM 80346. All protein sequences were subjected to BLAST analysis against the (b) (4) Database. The analysis results showed no pathogenicity-related genes in the production strain *C. glutamicum* KCCM 80346 (Appendix 2, Attachment 5).

2) Potential for DNA transfer or any capacity for enhanced gene transfer

To prevent any potential transfer of genetic material to other organisms, the strategy of construction for *C. glutamicum* KCCM 80346 strain was based on procedures described below.

- Any genetic material including plasmid to be autonomously replicable was not used.

- All the genetic modifications were done on the chromosome.

3) Resistance of antibiotics of the production strain

The antibiotic minimum inhibitory concentration (MIC) for the Dried L-Tryptophan Fermentation Product production strain was observed. The broth dilution method was used to determine the susceptibility of the production strain *C. glutamicum* KCCM 80346. In regard to antibiotic resistance, *C. glutamicum* wild-type strains has not been reported to have any antibiotic resistance. This was confirmed by the minimum inhibitory concentration (MIC) test and study report is provided in Appendix 2, Attachment 2. *C. glutamicum* KCCM 80346 showed same susceptibility to antibiotics with the wild-type *C. glutamicum* (b) (4). These results support that antibiotic resistance genes do not exist on the chromosome of the *C. glutamicum* KCCM 80346.

4) Absence of viable cell in final product

The absence of viable cells of the production strain in the Dried L-Tryptophan Fermentation Product was examined in accordance with the European Food Safety Authority guidance (EFSA, 2018). According to this study, no viable cells were observed in the final product and manufacturing processes after cell inactivation of the fermentation broth (Appendix 2, Attachment 3).

6.3 Safety Considerations for L-Tryptophan

Dried L-Tryptophan Fermentation Product is a source of nutritional L-tryptophan that can be safely used in the production of proteins like all other sources of L-tryptophan.

L-Tryptophan is codified as a Generally Recognized as Safe amino acid for the use in animal feed (21 CFR §582.5915). L-Tryptophan is an essential amino acid, as discussed in Section 2 and is formulated in diets based on potential natural deficiencies.

The European Food Safety Authority's (EFSA) Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) has reviewed the safety and efficacy of L-tryptophan when used in animal diets (EFSA, 2015). According to this report, L-tryptophan additives in animal feed are incorporated into the proteins of tissues and/or products of target animal species, and L-tryptophan that exceeds the tryptophan requirement of the animal is excreted as urea/uric acid and carbon dioxide. Consequently, no free L-tryptophan occurs or accumulates in target animal tissues. L-Tryptophan is an essential amino acid for humans. There is no residue issue in free L-tryptophan. Therefore, Dried L-Tryptophan Fermentation Product presents no exposure risk to humans consuming tissues or products from the target animal species.

6.4 Safety Considers of Dried L-Tryptophan Fermentation Product

As seen in Table 2.1 and Appendix 1, the majority of the substances in the product are typical components of swine feed.

To corroborate the safety of Dried L-Tryptophan Fermentation Product, the potential sub-chronic toxicity of Dried L-Tryptophan Fermentation Product in rats followed by a 4-week recovery period was conducted in accordance with ‘Repeated Dose 90-Day Oral Toxicity Study in Rodents (OECD, 2018)’. In this study, Dried L-Tryptophan Fermentation Product was administered daily by oral gavage at doses of 0, 500, 1000, and 2000 mg/kg/day to groups of 10 male and 10 female Wistar Han IGS rat for 13 weeks. For the groups that were administered doses of 0 and 2000 mg/kg/day, an additional 5 male and 5 female SD rats were tested as a recovery group. No adverse effects associated with the test substance were

observed in male or female Wistar Han IGS rat after 13 weeks of administration at dosages of 0, 500, 1000, and 2000 mg/kg/day and 4 weeks of recovery at dosages of 0 and 2000 mg/kg/day. Therefore, the no-observed-adverse-effect level of the dried L-tryptophan fermentation product was determined to be 2000 mg/kg/day (the highest tested dose) in both sexes. Full study report is provided as Appendix 7.

Additionally, the potential mutagenicity of Dried L-Tryptophan Fermentation Product was evaluated in accordance with 'Bacterial Reverse Mutation Assay (OECD, 1997)'. This study was conducted using *Salmonella typhimurium* strains TA98, TA100, TA102, Ta1535 and TA1537 in the absence and presence of a post mitochondrial supernatant (S9 fraction) from the livers of phenobarbital/β-naphthoflavone-induced rats. Dried L-Tryptophan Fermentation Product showed no evidence of mutagenicity in this test. Full study report is provided as Appendix 8.

6.5 Safety Assessment of Non-Tryptophan Components and Impurities

6.5.1 Assessment of Non-Tryptophan Composition

The GRAS substance is 60% L-tryptophan with specifications permitting up to 5% moisture and 10% ash. Section 3 of this dossier suggests the maximum level of use in the diet as 0.37% (0.22% L-tryptophan) of feed. Table 6.1 provides the compositional analysis and, by calculation, considers the contribution of this level of use in a complete diet.

Table 6.1. Contribution of non-L-tryptophan components when Dried L-Tryptophan Fermentation Product incorporated into a complete feed at 0.37%

Substance	Average level in Dried L-Tryptophan Fermentation Product (%)	Contribution of the Dried L-Tryptophan Fermentation Product incorporated in feed at 0.37% (ppm)
Crude ash	7.8	(b) (4)
Crude fat B (with HCl)	3.4	
Starch	<0.2	
Total sugars calc. as sucrose	4.8	
Crude fiber	<0.5	
Total nucleic acids	0.64	
Other amino acids	13.48	
Crude ash	7.8	
Substance	**Average level in Dried L-Tryptophan Fermentation Product (ppm)**	**Contribution of the Dried L-Tryptophan Fermentation Product incorporated in feed at 0.37% (ppb)**
Lead	0.025	(b) (4)
Cadmium	< 0.010	
Mercury	< 0.010	

Substance	Average level in Dried L-Tryptophan Fermentation Product (%)	Contribution of the Dried L-Tryptophan Fermentation Product incorporated in feed at 0.37% (ppm)
Arsenic	0.147	(b) (4)

The levels of non-L-tryptophan components are consistent with nutritional components of conventional feedstuffs, and the non-nutritional components are well below any potential safety concern and consistent with other fermentation product components.

6.5.2 Assessment of Biogenic Amines

Biogenic amines are biogenic substances with one or more amine groups. They are basic nitrogenous compounds formed mainly by decarboxylation of amino acids or by amination and transamination of aldehydes and ketones. CJ analyzed for typical biogenic amines; 2-phenethylamine, cadaverine, histamine, putrescine, spermidine, spermine, tryptamine, and tyramine in three batches of Dried L-Tryptophan Fermentation Product.

The potential biogenic amines were also analyzed in the fermentation broths comparing against the wild-type strain (*C. glutamicum* (b) (4)) and production strain (*C. glutamicum* KCCM 80346). This data can be found in Appendix 2. Pre-fermentation. These data indicate that the genetic alterations did not impact the levels of biogenic amines.

Analysis of the Dried L-Tryptophan Fermentation Product demonstrated a similar amount of each biogenic amine was detected in the three independent batches of Dried L-Tryptophan Fermentation Product (Table 6.2). The analytical data is provided in Appendix 10. The levels of the tested biogenic amines ranged from <1-11600 mg/kg in the final product. The level of tryptamine was significantly higher than that of other biogenic amines. It might be caused from the existence of high concentration of L-tryptophan after fermentation which is a precursor of tryptamine. Additional biogenic amine synthesis may continue during the fermentation broth storage and pH adjustment step after fermentation, which is a decarboxylation reaction of converting tryptophan into tryptamine. So, tryptamine level may increase in the test samples.

Table 6.2. Biogenic amines in Dried L-Tryptophan Fermentation Product

Parameter	Batch		
	(b) (4)		
Phenylethylamine (mg/kg)			
Cadaverine (mg/kg)			
Histamine (mg/kg)			
Putrescine (mg/kg)			
Spermidine (mg/kg)			
Spermine (mg/kg)			
Tryptamine (mg/kg)			

Parameter	Batch		
	(b) (4)		
Tyramine (mg/kg)	(b) (4)		
Total	**11290.1**	**12310.06**	**11106.19**

Biogenic amines maybe present in fermented foods (whether or not fermented intentionally (spoilage)) and ingredients derived from fermentation. Studies have considered the potential concerns of biogenic amines in animal safety. Bermudez and Firman (1998) fed poultry diets supplemented with 292 ppm biogenic amines (four different biogenic amines) and found no significant response on performance, gross lesions, or histological evidence when measured after feeding for 2, 4, and 6 weeks. In a review article Feddern et al. (2019), examined US sources of animal by-product meals for a total of five biogenic amines. They reported average total of the five biogenic amines ranging from 245 ppm (meat and bone meal) - 822 ppm (poultry meal). Given the upper exposure limit outlined Section 3 of the notice (0.37% of the complete feed), the level of specific biogenic amines would range from 3.7 ppb to 42.92 ppm. Using the highest level (worst case) of the analyzed eight biogenic amines (from Table 6.3) the calculated addition to the complete feed is 45.55 ppm. This level is 6.41 X lower than the levels which Bermudez and Firman (1998) found had no impact on poultry growth and health. Hence, the amount of biogenic amines (45.55 ppm) provided by Dried L-Tryptophan Fermentation Product to swine diet is numerically and biologically insignificant and would not cause a safety concern. The exposure of swine to these insignificant levels of biogenic amines (especially in comparison to the typical dietary ingredients) and will not impact target animal safety or human food safety.

6.5.3 Assessment of L-Tryptophan Impurities

It has been reported in 1989 that the use of L-tryptophan for human dietary supplement was raised the safety concern called Eosinophilia-Myalgia Syndrome (EMS). However, all reported cases of EMS were caused by consumption certain batches produced by a single manufacturer and it deemed to be caused by impurities that occurred during the changes in L-tryptophan manufacturing process. The main causative components have been verified and those are (1) 3-phenylaminoalanine (PAA), (2) 1,1'-ethylidenebistryptophan (EBT), (3) 2(3-indoylmethyl)-L-tryptophan (IMT), (4) 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid (PIC), (5) 2-(2-hydroxyindoline)-tryptophan (HIT), and (6) (S)-2-amino-3-(2-((S,E)-7-methylnon-1-en-1-yl)-1H-indol-3-yl) propanoic acid, or (S)-2-amino-3-(2-((E)-dec-1-en-1-yl)-1H-indol-3-yl) propanoic acid (AAA).

CJ analyzed for above mentioned impurities in three batches of Dried L-Tryptophan Fermentation Product. Also, two additional compounds were analyzed, (S)-2-amino-3-(5-hydroxy-1H-indol-3-yl)propanoic acid (HTP) and 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA). (S)-2-amino-3-(5-hydroxy-1H-indol-3-yl)propanoic acid (HTP) can be used as a substitute for L-tryptophan in physiological metabolism and 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA) is a known derivative of L-tryptophan which is synthesized from 1,1'-ethylidenebistryptophan. This data can be found in Appendix 9. The existence of four components, 2(3-indoylmethyl)-L-tryptophan (IMT), 3a-

hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid (PIC), (S)-2-amino-3-(5-hydroxy-1H-indol-3-yl)propanoic acid (HTP), and 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA), in the Dried L-Tryptophan Fermentation Product were confirmed by qualitative analysis and the level of each component was analysed. The levels of the existed L-tryptophan impurities ranged from 399.53-791.41 mg/kg in the final product.

Table 6.3. L-tryptophan impurities in Dried L-Tryptophan Fermentation Product

Parameter	Batch		
	(b) (4)		
HTP (mg/kg)			
IMT (mg/kg)			
MTCA (mg/kg)			
PIC (mg/kg)			
Total	**399.53**	**791.41**	**546.88**

Simat et al. (2003) analyzed the impurities of L-tryptophan including potential EMS-related substances in pharmaceutical- and feed-grade of L-tryptophan from the market which has no impact on safety to human and animals, as well as the batch of EMS associated L-tryptophan. Notably, no EBT except EMS associated L-tryptophan was detected, either in pharma- or feed-grade L-tryptophan. The total level of four impurities which existed in test samples ranged from 15.8 to 2469.9 mg/kg and from 235.5 to 5492.7 mg/kg for pharmaceutical-grade and feed-grade, respectively. In Dried L-Tryptophan Fermentation Product, total level of impurities of L-tryptophan is 6.9 X lower than the levels that Simat et al. (2003) reported. Therefore, the amount of L-tryptophan impurities provided by Dried L-Tryptophan Fermentation Product to swine diet is numerically and biologically insignificant and would not cause a safety concern. The exposure of swine to these insignificant levels of L-tryptophan impurities (especially in comparison to the commercially available L-tryptophan) and will not impact target animal safety or human food safety.

An animal study was conducted to examine the impact of L-tryptophan and its impurities on humans who consume meat products derived from animals fed Dried L-Tryptophan Fermentation Product. The study observed the occurrence of toxicological or EMS-related symptoms and analyzed the residues of L-tryptophan impurities in meat products. The outcome of this investigation showed no evidence of adverse effects associated with Dried L-Tryptophan Fermentation Product. Additionally, the majority of impurities of L-tryptophan were not found in the edible tissues. Details of the animal study can be found in Appendix 9.

6.6 Safety Assessment for Target Animals

The notice covers the safety of the Dried L-Tryptophan Fermentation Product from a number of perspectives. Section 6.1 covers the known safety of the host species *C. glutamicum* based on the review of literature and previous safety determinations by FDA and other authoritative bodies. The genetic modification process was exhaustively assessed to demonstrate that no unexpected changes would impact the safety of the GRAS substance (Section 6.2 and Appendix 2). The history of use and regulatory status of L-tryptophan was provided in Section 6.3 of the notice. The dossier includes both the report of the sub-chronic oral toxicity test and the Bacterial Reverse Mutation Assay, which further supported the safety determination (Section 6.4). Table 2.5 provides the heavy metal levels of the fermentation product which are very low, well below concern level (NRC, 2005) based on the fact that the starting materials are feed grade and have specific tight specifications. The notice includes a compositional analysis as well as the analysis on the possible contamination through biogenic amines and EMS-related compounds (Section 6.5); that demonstrates that the levels of impurities will not impact the safety of the GRAS substance. The notice provides the basis of CJ's determination that there is reasonable certainty that the Dried L-Tryptophan Fermentation Product as a source of L-tryptophan for swine is not harmful and that the conclusion meets the generally recognized as safe standard. We are not aware of any additional information and data that are or may appear to be inconsistent with our conclusion of GRAS status.

6.7 Safety Assessment for Human Consumption

Dried L-Tryptophan Fermentation Product is intended for use as a nutrient for animal consumption. Ordinarily, a GRAS notice will address the potential human dietary consumption of a component of animal feed due to consumption of animal products and tissues in which the component may be present. In this case, however, there is no need to determine the estimated daily intake (EDI) of the Dried L-Tryptophan Fermentation Product for human consumption. L-tryptophan (Dried L-Tryptophan Fermentation Product) and any of the described non-L-tryptophan components shown in Table 6.1 above will be metabolized when the animal consumes and digests animal feed containing Dried L-Tryptophan Fermentation Product. Dried L-Tryptophan Fermentation Product derived from the genetically modified *C. glutamicum* will be indistinguishable from other L-tryptophan sources, as will be the potential non L-tryptophan components, which are all normal components of animal feed. Non-tryptophan components of Dried L-Tryptophan Fermentation Product are all typical feed components, mostly nutrients and will not be a concern for residues.

This same determination was made by the FDA in their support of the AAFCO definition 36.16 Dried L-Lysine Fermentation Product (AAFCO, 2018), 36.17 Liquid L-Lysine Fermentation product (AAFCO, 2018) and 36.1 Condensed Extracted Glutamic Acid Fermentation Product (AAFCO, 2018).

In this regard, the European Food Safety Authority's (EFSA) Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) has reviewed the safety and efficacy of L-tryptophan

produced by fermentation for use in the diets of all animal species (EFSA, 2013, 2015 and 2019). According to this report, L-tryptophan additives in animal feed will be incorporated into proteins of tissues and/or products of target animal species. Also, doses exceeding the L- tryptophan requirement of the animal will be excreted as urea/uric acid, indole-related compounds and carbon dioxide. Consequently, no free L-tryptophan occurs or accumulates in target animal tissues and the only form of L-tryptophan that humans will be exposed to from its use in animal feed is in the form of protein that will be digested, absorbed, and metabolized consistent with human nutrient needs. The absence of residual L-tryptophan in the tissues of animals consuming L-tryptophan in its diet will, therefore, not result in a subsequent human exposure or safety issue. As indicated by the analytical values displayed in Table 2.1, Table 6.1, and Appendix 1, residual components of Dried L-Tryptophan Fermentation Product are at levels too low to present any risk of humans consuming the tissues of food animals fed the nutrient. All residual constituents are common metabolites or minerals and will be either excreted or metabolized. Therefore, they present no exposure risk to humans consuming tissues or products from the target animal. A review of the publicly available literature does not reveal information demonstrating that any of these residual constituents appears to present a risk of accumulation or harm to humans at the levels that would be consumed from animal tissue (Meyers et al., 2006). It should also be noted that L-tryptophan is an essential amino acid for human nutrition is approved for direct addition to human food (21 CFR §172.320).

Since Dried L-Tryptophan Fermentation Product produced by fermentation with *C. glutamicum* KCCM 80346, potential impurities occurring during the fermentation were analyzed additionally. These impurities: biogenic amines (Section 6.5.2) and EMS-related compounds (Section 6.5.3) are all well below safety concerns and are consistent with other feedstuffs offered to swine.

As such there is no hazard specific to these potential derivatives nor any other compounds as assessed by CJ in the full description of the GRAS substance. CJ has reasonable certainty that the substance is not harmful under the conditions of its intended use for humans consuming the products from animals provided Dried L-Tryptophan Fermentation product.

6.8 Safety Conclusion

Based on the documentation provided in this GRAS Notification and as discussed above, CJ concludes that Dried L-Tryptophan Fermentation Product produced by fermentation with *C. glutamicum* is generally recognized as safe via scientific procedures as a nutrient for animal consumption. CJ has reasonable certainty that the substance is not harmful under the conditions of its intended use. The notifier has reviewed the available data and information and is not aware of any data and information that is, or may appear to be, inconsistent with our conclusion of GRAS status.

Part 7 GRAS Notice: List of Supporting Data and Information

7.1 Confidential Information

The only information that is considered confidential in this GRAS Notice is the information specific to the production of the genetically modified organism, the manufacturing process, and the documentation of the analytical method. However, the safety narrative provides the complete analytical results. All this information is provided on a summary basis in the body of the submission, as required by 21 CFR §570 Subpart E. Therefore, the summary of the manufacturing process, with the full disclosure of the safety assessment, are consistent with the general recognition standards.

7.2 Supporting Data Information

All submitted data and reports were tested with samples produced on a pilot scale in CJ R&D center. The production process is the same for both the pilot scale and the commercial scale, ensuring that the identity of the final product is the same regardless of the scale.

7.3 References

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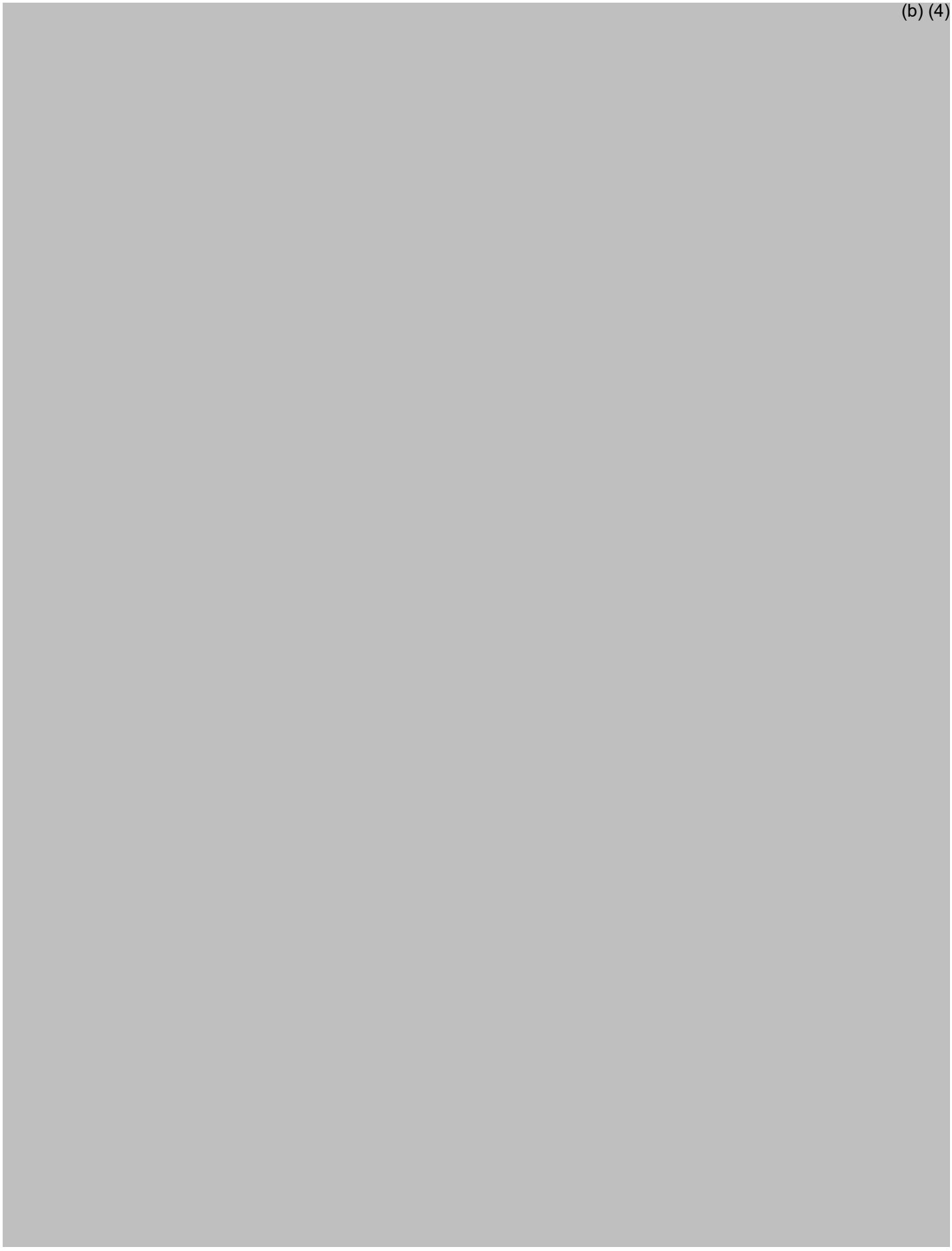
(b) (4)

(b) (4)

Sampler: by client

Parameter	Unit	Results in original substance
Moisture *VO (EG) 152 Annex III, A; 2009*	%	(b) (4)
Ammonium Nitrogen (NH_4-N) *VDLUFA II, 3.2.6, 1995; #6*	mg/kg	
Crude ash *VO (EG) 152 Annex III, M; 2009*	%	
Crude protein (N x 6,25) *VO (EG) 152 Annex III, C; 2009*	%	
Crude fat B (with HCl) *VO (EG) 152 Annex III, H; 2009*	%	
Starch *VO (EG) 152 Annex III, L; 2009*	%	
Total sugars calc. as sucrose *VO (EG) 152 Annex III, J; 2009*	%	
Crude fibre *VO (EG) 152 Annex III, I; 2009*	%	
Tryptophan *VO (EG) 152/2009, Anhang III, G*	%	
Chloride (Cl^-) *VDLUFA III 10.5.2; 1976*	%	
Calcium (Ca) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	
Phosphorus (P) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	
Sodium (Na) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	
Potassium (K) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	

(b) (4)


(b) (4)


(b) (4)


(b) (4)


(b) (4)

(b) (4)

Sampler: by client

Parameter	Unit	Results in original substance
Lysine *VO (EG) 152/2009, Anhang III, F; #5*	%	(b) (4)
Methionine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Cystine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Asparagine Acid *VO (EG) 152/2009, Anhang III, F; #5*	%	
Threonine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Serine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Glutamic acid *VO (EG) 152/2009, Anhang III, F; #5*	%	
Proline *VO (EG) 152/2009, Anhang III, F; #5*	%	
Glycine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Alanine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Valine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Isoleucine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Leucine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Tyrosine *VO (EG) 152/2009, Anhang III, F; #5*	%	

(b) (4)

(b) (4)

Parameter	Unit	Results in original substance
Phenylalanin *VO (EG) 152/2009, Anhang III, F; #5*	%	(b) (4)
Histidine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Arginin *VO (EG) 152/2009, Anhang III, F; #5*	%	

(b) (4)

(b) (4)

The parameters have the following LOQ´s:

Parameter	(b) (4)
Lysine	
Methionine	
Cysteine	
Asparagine acid	
Threonine	
Serine	
Glutamc acid	
Proline	
Glycine	
Alanine	
Valine	
Isoleucine	
Leucine	
Tyrosine	
Phenylalanin	
Histidine	
Arginin	

In this sample, no results can be given for aspartic acid and histidine, because the quantitative evaluation of the measurements is not possible due to the high tryptophan content of the sample.

(b) (4)


(b) (4)


(b) (4)

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Certificate No.	2023-PR-230	Receipt No.	2023-AN-200
Client	-	Date of Receipt	2023.07.04.
Client Name	-	Date of Test	2023.07.04.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	Dried L-Tryptophan Fermentation Product (TRP Pro)		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		

Test Item(s)	Test result	Test method used
nucleoside & nucleotide	(b) (4)	Schmidt-Thannhauser-Schneider(STS) method (carried out for insoluble part)
DNA		
RNA		

* Information

(b) (4), (b)(6)

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(b) (4)

Sampler: by client

Parameter	Unit	Results in original substance
Moisture *VO (EG) 152 Annex III, A; 2009*	%	(b) (4)
Ammonium Nitrogen (NH_4-N) *VDLUFA II, 3.2.6, 1995; #6*	mg/kg	
Crude ash *VO (EG) 152 Annex III, M; 2009*	%	
Crude protein (N x 6,25) *VO (EG) 152 Annex III, C; 2009*	%	
Crude fat B (with HCl) *VO (EG) 152 Annex III, H; 2009*	%	
Starch *VO (EG) 152 Annex III, L; 2009*	%	
Total sugars calc. as sucrose *VO (EG) 152 Annex III, J; 2009*	%	
Crude fibre *VO (EG) 152 Annex III, I; 2009*	%	
Tryptophan *VO (EG) 152/2009, Anhang III, G*	%	
Chloride (Cl^-) *VDLUFA III 10.5.2; 1976*	%	
Calcium (Ca) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	
Phosphorus (P) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	
Sodium (Na) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	
Potassium (K) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	

(b) (4)

(b) (4)

Parameter	Unit	Results in original substance
Sulphur (S) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	(b) (4)

The parameters have the following LOQ´s:

Parameter	LOQ
Calcium	(b) (4)
Phosphorus	
Sodium	
Potassium	
Sulphur	
Moisture	
Crude protein	
Crude fat	
Crude ash	
Crude fibre	
Starch	
Sugar	
Chloride	
NH4-N	
Tryptophan	

(b) (4)


(b) (4)


(b) (4)

(b) (4)

Sampler: by client

Parameter	Unit	Results in original substance
Lysine *VO (EG) 152/2009, Anhang III, F; #5*	%	(b) (4)
Methionine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Cystine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Asparagine Acid *VO (EG) 152/2009, Anhang III, F; #5*	%	
Threonine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Serine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Glutamic acid *VO (EG) 152/2009, Anhang III, F; #5*	%	
Proline *VO (EG) 152/2009, Anhang III, F; #5*	%	
Glycine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Alanine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Valine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Isoleucine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Leucine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Tyrosine *VO (EG) 152/2009, Anhang III, F; #5*	%	

(b) (4)

(b) (4)

Parameter	Unit	Results in original substance
Phenylalanin *VO (EG) 152/2009, Anhang III, F; #5*	%	(b) (4)
Histidine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Arginin *VO (EG) 152/2009, Anhang III, F; #5*	%	

(b) (4)

(b) (4)

The parameters have the following LOQ´s:

Parameter	**LOQ** (b) (4)
Lysine	
Methionine	
Cysteine	
Asparagine acid	
Threonine	
Serine	
Glutamc acid	
Proline	
Glycine	
Alanine	
Valine	
Isoleucine	
Leucine	
Tyrosine	
Phenylalanin	
Histidine	
Arginin	

In this sample, no results can be given for aspartic acid and histidine, because the quantitative evaluation of the measurements is not possible due to the high tryptophan content of the sample.

(b) (4)


(b) (4)


(b) (4)

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Certificate of analysis

Certificate No.	2023-PR-231	Receipt No.	2023-AN-201
Client	-	Date of Receipt	2023.07.04.
Client Name	-	Date of Test	2023.07.04.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	Dried L-Tryptophan Fermentation Product (TRP Pro)		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		

Test Item(s)	Test result	Test method used
nucleoside & nucleotide	(b) (4)	Schmidt-Thannhauser-Schneider(STS) method (carried out for insoluble part)
DNA		
RNA		

* Information

(b) (4), (b)(6)

21, 2023

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(b) (4)

Sampler: by client

Parameter	Unit	Results in original substance
Moisture *VO (EG) 152 Annex III, A; 2009*	%	(b) (4)
Ammonium Nitrogen (NH_4-N) *VDLUFA II, 3.2.6, 1995; #6*	mg/kg	
Crude ash *VO (EG) 152 Annex III, M; 2009*	%	
Crude protein (N x 6,25) *VO (EG) 152 Annex III, C; 2009*	%	
Crude fat B (with HCl) *VO (EG) 152 Annex III, H; 2009*	%	
Starch *VO (EG) 152 Annex III, L; 2009*	%	
Total sugars calc. as sucrose *VO (EG) 152 Annex III, J; 2009*	%	
Crude fibre *VO (EG) 152 Annex III, I; 2009*	%	
Tryptophan *VO (EG) 152/2009, Anhang III, G*	%	
Chloride (Cl^-) *VDLUFA III 10.5.2; 1976*	%	
Calcium (Ca) *ASU F 0096; 2019-06, #A1*	%	
Phosphorus (P) *ASU F 0096; 2019-06, #A1*	%	
Sodium (Na) *ASU F 0096; 2019-06, #A1*	%	
Potassium (K) *ASU F 0096; 2019-06, #A1*	%	

(b) (4)

(b) (4)

The parameters have the following LOQ´s:

Parameter	LOQ
Calcium	(b) (4)
Phosphorus	
Sodium	
Potassium	
Sulphur	
Moisture	
Crude protein	
Crude fat	
Crude ash	
Crude fibre	
Starch	
Sugar	
Chloride	
NH4-N	
Tryptophan	

(b) (4)


(b) (4)


(b) (4)

(b) (4)

Sampler: by client

Parameter	Unit	Results in original substance
Lysine *VO (EG) 152/2009, Anhang III, F; #5*	%	(b) (4)
Methionine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Cystine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Asparagine Acid *VO (EG) 152/2009, Anhang III, F; #5*	%	
Threonine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Serine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Glutamic acid *VO (EG) 152/2009, Anhang III, F; #5*	%	
Proline *VO (EG) 152/2009, Anhang III, F; #5*	%	
Glycine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Alanine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Valine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Isoleucine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Leucine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Tyrosine *VO (EG) 152/2009, Anhang III, F; #5*	%	

(b) (4)


(b) (4)


(b) (4)

(b) (4)

The parameters have the following LOQ´s:

Parameter	**LOQ**
Lysine	(b) (4)
Methionine	
Cysteine	
Asparagine acid	
Threonine	
Serine	
Glutamc acid	
Proline	
Glycine	
Alanine	
Valine	
Isoleucine	
Leucine	
Tyrosine	
Phenylalanin	
Histidine	
Arginin	

In this sample, no results can be given for aspartic acid and histidine, because the quantitative evaluation of the measurements is not possible due to the high tryptophan content of the sample.

(b) (4)


(b) (4)


(b) (4)

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Certificate of analysis

Certificate No.	2023-PR-232	Receipt No.	2023-AN-202
Client	-	Date of Receipt	2023.07.04.
Client Name	-	Date of Test	2023.07.04.
Client Tel	-	Use of Report	Reference test
Client Address	-		

Test Sample	Dried L-Tryptophan Fermentation Product (TRP Pro)
Manuf. Date	2021.10.07
Lot. No	(b) (4)

Test Item(s)	Test result	Test method used
nucleoside & nucleotide	(b) (4)	Schmidt-Thannhauser-Schneider(STS) method (carried out for insoluble part)
DNA		
RNA		

* Information

(b) (4), (b)(6)

, 21, 2023

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(b) (4)

Sampler: by client

Parameter	Unit	Results in original substance
Moisture *VO (EG) 152 Annex III, A; 2009*	%	(b) (4)
Ammonium Nitrogen (NH_4-N) *VDLUFA II, 3.2.6, 1995; #6*	mg/kg	
Crude ash *VO (EG) 152 Annex III, M; 2009*	%	
Crude protein (N x 6,25) *VO (EG) 152 Annex III, C; 2009*	%	
Crude fat B (with HCl) *VO (EG) 152 Annex III, H; 2009*	%	
Starch *VO (EG) 152 Annex III, L; 2009*	%	
Total sugars calc. as sucrose *VO (EG) 152 Annex III, J; 2009*	%	
Crude fibre *VO (EG) 152 Annex III, I; 2009*	%	
Tryptophan *VO (EG) 152/2009, Anhang III, G*	%	
Chloride (Cl^-) *VDLUFA III 10.5.2; 1976*	%	
Calcium (Ca) *ASU F 0096; 2019-06, #A1*	%	
Phosphorus (P) *ASU F 0096; 2019-06, #A1*	%	
Sodium (Na) *ASU F 0096; 2019-06, #A1*	%	
Potassium (K) *ASU F 0096; 2019-06, #A1*	%	

(b) (4)

(b) (4)

Parameter	Unit	Results in original substance
Sulphur (S) *ASU F 0096; 2019-06, #A1*	%	(b) (4)

The parameters have the following LOQ´s:

Parameter	LOQ
Calcium	(b) (4)
Phosphorus	
Sodium	
Potassium	
Sulphur	
Moisture	
Crude protein	
Crude fat	
Crude ash	
Crude fibre	
Starch	
Sugar	
Chloride	
NH4-N	
Tryptophan	

(b) (4)


(b) (4), (b)(6)


(b) (4)

(b) (4)

Sampler: by client

Parameter	Unit	Results in original substance
Lysine *VO (EG) 152/2009, Anhang III, F; #5*	%	(b) (4)
Methionine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Cystine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Asparagine Acid *VO (EG) 152/2009, Anhang III, F; #5*	%	
Threonine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Serine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Glutamic acid *VO (EG) 152/2009, Anhang III, F; #5*	%	
Proline *VO (EG) 152/2009, Anhang III, F; #5*	%	
Glycine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Alanine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Valine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Isoleucine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Leucine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Tyrosine *VO (EG) 152/2009, Anhang III, F; #5*	%	

(b) (4)

(b) (4)

Parameter	Unit	Results in original substance
Phenylalanin *VO (EG) 152/2009, Anhang III, F; #5*	%	(b) (4)
Histidine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Arginin *VO (EG) 152/2009, Anhang III, F; #5*	%	

(b) (4)

(b) (4)

The parameters have the following LOQ´s:

Parameter	**LOQ**
Lysine	(b) (4)
Methionine	
Cysteine	
Asparagine acid	
Threonine	
Serine	
Glutamc acid	
Proline	
Glycine	
Alanine	
Valine	
Isoleucine	
Leucine	
Tyrosine	
Phenylalanin	
Histidine	
Arginin	

In this sample, no results can be given for aspartic acid and histidine, because the quantitative evaluation of the measurements is not possible due to the high tryptophan content of the sample.

(b) (4)

(b) (4)



(b) (4)



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Certificate of analysis

Certificate No.	2023-PR-233	Receipt No.	2023-AN-203
Client	-	Date of Receipt	2023.07.04.
Client Name	-	Date of Test	2023.07.04.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	Dried L-Tryptophan Fermentation Product (TRP Pro)		
Manuf. Date	2022.05.18.		
Lot. No	(b) (4)		

Test Item(s)	Test result	Test method used
nucleoside & nucleotide	(b) (4)	Schmidt-Thannhauser-Schneider(STS) method (carried out for insoluble part)
DNA		
RNA		

* Information

(b) (4), (b)(6)

e, 21, 2023

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(b) (4)

Sampler: by client

Parameter	Unit	Results in original substance
Moisture *VO (EG) 152 Annex III, A; 2009*	%	(b) (4)
Ammonium Nitrogen (NH_4-N) *VDLUFA II, 3.2.6, 1995; #6*	mg/kg	
Crude ash *VO (EG) 152 Annex III, M; 2009*	%	
Crude protein (N x 6,25) *VO (EG) 152 Annex III, C; 2009*	%	
Crude fat B (with HCl) *VO (EG) 152 Annex III, H; 2009*	%	
Starch *VO (EG) 152 Annex III, L; 2009*	%	
Total sugars calc. as sucrose *VO (EG) 152 Annex III, J; 2009*	%	
Crude fibre *VO (EG) 152 Annex III, I; 2009*	%	
Tryptophan *VO (EG) 152/2009, Anhang III, G*	%	
Chloride (Cl^-) *VDLUFA III 10.5.2; 1976*	%	
Calcium (Ca) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	
Phosphorus (P) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	
Sodium (Na) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	
Potassium (K) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	

(b) (4)

(b) (4)

Parameter	Unit	Results in original substance
Sulphur (S) *ASU F 0096; 2019-06 / DIN EN 15621; 2017-10, #A1*	%	(b) (4)

The parameters have the following LOQ´s:

Parameter	LOQ
Calcium	(b) (4)
Phosphorus	
Sodium	
Potassium	
Sulphur	
Moisture	
Crude protein	
Crude fat	
Crude ash	
Crude fibre	
Starch	
Sugar	
Chloride	
NH4-N	
Tryptophan	

(b) (4)

(b) (4)



(b) (4)



(b) (4)

Parameter	Unit	Results in original substance
Lysine *VO (EG) 152/2009, Anhang III, F; #5*	%	(b) (4)
Methionine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Cystine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Asparagine Acid *VO (EG) 152/2009, Anhang III, F; #5*	%	
Threonine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Serine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Glutamic acid *VO (EG) 152/2009, Anhang III, F; #5*	%	
Proline *VO (EG) 152/2009, Anhang III, F; #5*	%	
Glycine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Alanine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Valine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Isoleucine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Leucine *VO (EG) 152/2009, Anhang III, F; #5*	%	
Tyrosine *VO (EG) 152/2009, Anhang III, F; #5*	%	

(b) (4)


(b) (4)


(b) (4)

(b) (4)

The parameters have the following LOQ´s:

Parameter	**LOQ**
Lysine	(b) (4)
Methionine	
Cysteine	
Asparagine acid	
Threonine	
Serine	
Glutamc acid	
Proline	
Glycine	
Alanine	
Valine	
Isoleucine	
Leucine	
Tyrosine	
Phenylalanin	
Histidine	
Arginin	

In this sample, no results can be given for aspartic acid and histidine, because the quantitative evaluation of the measurements is not possible due to the high tryptophan content of the sample.

(b) (4)


(b) (4)


(b) (4)

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Certificate of analysis

Certificate No.	2023-PR-234	Receipt No.	2023-AN-204
Client	-	Date of Receipt	2023.07.04.
Client Name	-	Date of Test	2023.07.04.
Client Tel	-	Use of Report	Reference test
Client Address	-		

Test Sample	Dried L-Tryptophan Fermentation Product (TRP Pro)
Manuf. Date	2022.05.19.
Lot. No	

Test Item(s)	Test result	Test method used
nucleoside & nucleotide	(b) (4)	Schmidt-Thannhauser-Schneider(STS) method (carried out for insoluble part)
DNA		
RNA		

* Information

(b) (4), (b)(6)

, 21, 2023

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Attachment 1. Comparison crude protein and total amino acid content differences

In a pre-sub meeting with the FDA, a question was raised about the difference between the crude protein content and total amino acid content of Dried L-Tryptophan Fermented Product (Table 1). In response, we proved where this difference came from and demonstrated that the total nitrogen amount was not different by converting the nitrogen amount from the crude protein content and total amino acid content.

Table 1. Contents of crude protein and total amino acids in Dried L-Tryptophan Fermentation Product

	(b) (4)	Average
Crude Protein		**68.3**
Total Amino acids		**76.3**
Tryptophan		62.8
Lysine		0.87
Methionine		0.28
Cystine		0.12
Threonine		0.82
Serine		0.65
Glutamic acid		2.65
Proline		0.59
Glycine		0.84
Alanine		1.60
Valine		1.00
Isoleucine		0.78
Leucine		1.29
Tyrosine		0.48
Phenylalanine		0.63
Arginine		0.90

(b) (4)

Table 2. Nitrogen contents of amino acids

	Chemical formula	Molar mass (g mol^{-1})	Converted Nitrogen content (%)*

(b) (4)

	Chemical formula	Molar mass (g mol^{-1})	Converted Nitrogen content (%)*
(b) (4)			

* Nitrogen content was converted by applying a molar mass of nitrogen of 14.01.

(b) (4)

Table 3. Total nitrogen contents converted from the crude protein and total amino acid

Nitrogen content (unit, %)	(b) (4)	Average
from crude protein		10.93
from total amino acid		10.46

Therefore, we can conclude that the difference between crude protein and total amino acid content noted by CVM is due to the calculation of crude protein by multiplying it by a 6.25 conversion factor, which is a common factor, especially for products with a high content of certain amino acids such as our product, which does not reflect the nitrogen content of each amino acid, and we can argue that it is more appropriate to utilize the total amino acid analysis.

Reference

Elaine S. Krul, (2019), Calculation of Nitrogen-to-Protein Conversion Factors: A Review with a Focus on Soy Protein, JAOCS, 96(4) :339-364

[Supplementary Data]

Table S1. Converted nitrogen content from analytical values of total amino acids in Dried L-Tryptophan Fermentation Product

	(b) (4)	Average
Tryptophan	(b) (4)	8.62
Lysine		0.17
Methionine		0.03
Cystine		0.01
Threonine		0.10
Serine		0.09
Glutamic acid		0.25
Proline		0.07
Glycine		0.16
Alanine		0.25
Valine		0.12
Isoleucine		0.08
Leucine		0.14
Tyrosine		0.04
Phenylalanine		0.05
Arginine		0.29
Sum of nitrogen		**10.46**

CONFIDENTIAL REPORT

Analysis of antimicrobial resistance and virulence genes in *Herbaspirillum rhizosphaerae* and *Azotobacter vinelandii*

STUDY NO. (b) (4)

Version 1.0

Title

Analysis of antimicrobial resistance and virulence genes in *Herbaspirillum rhizosphaerae* and *Azotobacter vinelandii*

Objective

This study was conducted to analyze the antimicrobial resistance and virulence genes in *H. rhizosphaerae* and *A. vinelandii*.

Schedule of the study

Initiation of experiment: February 10, 2023

Termination of experiment: April 28, 2023

Submission of final report: May 12, 2023

Test facility

Digital & Technology, R&D, BIO, CJ CheilJedang

55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do 16495, Korea

Responsible personnel

Analyst	(b)(6)
Author	
Report approved by	

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3.1 Identification of antimicrobial resistance genes 4

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1. Introduction

Dried L-Tryptophan Fermentation Product is produced by fermentation with *Corynebacterium glutamicum* KCCM 80346. *C. glutamicum* KCCM 80346 was genetically modified to improve L-tryptophan production.

(b) (4)

2. Methods

2.1 Obtain genome sequences

Whole genome sequences for *H. rhizosphaerae* and *A. vinelandii* were obtained from NCBI (National Center for Biotechnology Information) genome database. The NCBI reference sequences for *H. rhizosphaerae* and *A. vinelandii* strains used in this analysis are (b) (4).

2.2 Identification of antimicrobial resistance (AMR) genes

(b) (4)

3. Results

3.1 Identification of antimicrobial resistance genes

(b) (4)

(b) (4)

(b) (4)

(b) (4)



4. References

[1] Bortolaia V et al. 2020. ResFinder 4.0 for predictions of phenotypes from genotypes. *J Antimicrob Chemother*. 75(12): 3491–3500.

[2] Florensa AF et al. 2022. ResFinder - an open online resource for identification of antimicrobial resistance genes in next-generation sequencing data and prediction of phenotypes from genotypes. *Microb Genom*. 8:000748.

[3] EFSA, 2020. Scientific Opinion on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA (2017–2019). EFSA Journal. 2020; 18(2):5966. Available online: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2020.5966

[4] Kleinheinz KA et al. 2014. Applying the ResFinder and VirulenceFinder web-services for easy identification of acquired antibiotic resistance and *E. coli* virulence genes in bacteriophage and prophage nucleotide sequences. *Bacteriophage*. 4:e27943.

[5] Tetzschner AMM et al. 2020. In silico genotyping of *Escherichia coli* isolates for extraintestinal virulence genes by use of whole-genome sequencing data. *J Clin Microbiol*. 58(10):e01269-20.

CONFIDENTIAL REPORT

Analysis of antimicrobial resistance and virulence genes in *Herbaspirillum rhizosphaerae* and *Azotobacter vinelandii*

STUDY NO. (b) (4)

Version 1.0

Title

Analysis of antimicrobial resistance and virulence genes in *Herbaspirillum rhizosphaerae* and *Azotobacter vinelandii*

Objective

This study was conducted to analyze the antimicrobial resistance and virulence genes in *H. rhizosphaerae* and *A. vinelandii*.

Schedule of the study

Initiation of experiment: February 10, 2023

Termination of experiment: April 28, 2023

Submission of final report: May 12, 2023

Test facility

Digital & Technology, R&D, BIO, CJ CheilJedang

55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do 16495, Korea

Responsible personnel

Analyst	(b)(6)
Author	
Report approved by	

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3. Results **4**

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4. References **8**

1. Introduction

Dried L-Tryptophan Fermentation Product is produced by fermentation with *Corynebacterium glutamicum* KCCM 80346. *C. glutamicum* KCCM 80346 was genetically modified to improve L-tryptophan production.

(b) (4)

2. Methods

2.1 Obtain genome sequences

Whole genome sequences for *H. rhizosphaerae* and *A. vinelandii* were obtained from NCBI (National Center for Biotechnology Information) genome database. The NCBI reference sequences for *H. rhizosphaerae* and *A. vinelandii* strains used in this analysis are (b) (4).

2.2 Identification of antimicrobial resistance (AMR) genes

(b) (4)

3. Results

3.1 Identification of antimicrobial resistance genes

(b) (4)

(b) (4)

(b) (4)

(b) (4)



4. References

[1] Bortolaia V et al. 2020. ResFinder 4.0 for predictions of phenotypes from genotypes. *J Antimicrob Chemother*. 75(12): 3491–3500.

[2] Florensa AF et al. 2022. ResFinder - an open online resource for identification of antimicrobial resistance genes in next-generation sequencing data and prediction of phenotypes from genotypes. *Microb Genom*. 8:000748.

[3] EFSA, 2020. Scientific Opinion on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA (2017–2019). EFSA Journal. 2020; 18(2):5966. Available online: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2020.5966

[4] Kleinheinz KA et al. 2014. Applying the ResFinder and VirulenceFinder web-services for easy identification of acquired antibiotic resistance and *E. coli* virulence genes in bacteriophage and prophage nucleotide sequences. *Bacteriophage*. 4:e27943.

[5] Tetzschner AMM et al. 2020. In silico genotyping of *Escherichia coli* isolates for extraintestinal virulence genes by use of whole-genome sequencing data. *J Clin Microbiol*. 58(10):e01269-20.

CONFIDENTIAL REPORT

Determination of antibiotic minimum inhibitory concentration (MIC) of *C. glutamicum* KCCM 80346

Version 1.0

TITLE

Determination of antibiotic minimal inhibitory concentration (MIC) of *Corynebacterium glutamicum* (b) (4)

OBJECTIVE OF THE STUDY

This study was conducted to determine MIC of TRP Pro producing strain *C. glutamicum* KCCM 80346.

SCHEDULE OF THE STUDY

Initiation of experiment: August 24, 2021

Termination of experiment: September 1, 2021

Submission of final report: September 10, 2021

TESTING FACILITY

R&BD)Regulatory Affairs, CJ CheilJedang
55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do 16495, Korea

RESPONSIBLE STAFFS

	(b)(6)
Analyst and Author	
Report approved by	

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Preparation of inoculum 5

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INTRODUCTION

Corynebacterium glutamicum KCCM 80346 used as a production microorganism of L-tryptophan. In order to observe antimicrobial susceptibility, minimum inhibitory concentration (MIC) test of *C. glutamicum* KCCM 80346 was conducted by (b) (4)

(b) (4)

MATERIALS AND METHODS

The MIC of production strain was evaluated in accordance with the broth microdilution method given in the Clinical and Laboratory Standards Institute (CLSI) guideline [1].

Preparation of antibiotics solution

(b) (4)


(b) (4)

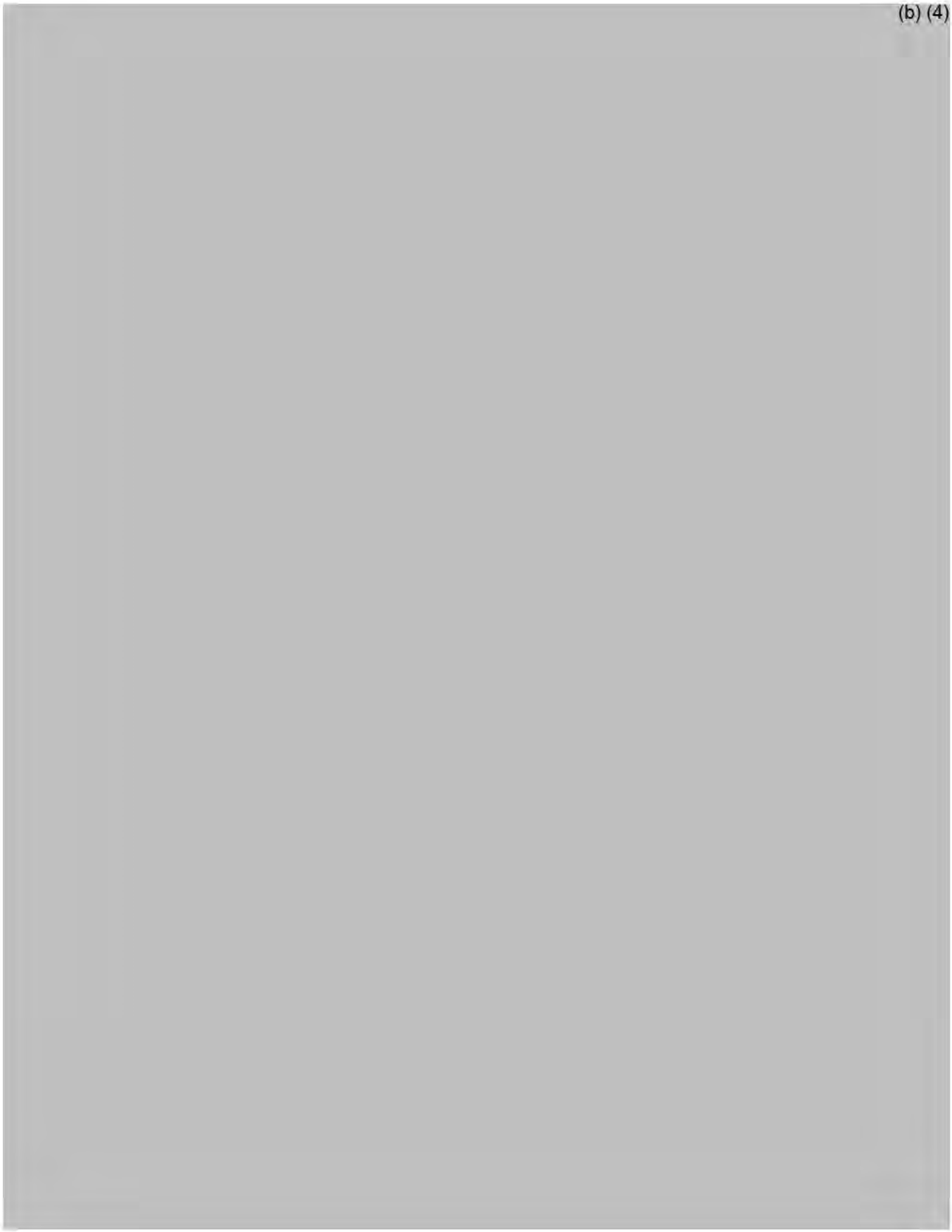
RESULTS

Since the production strain is belonging to *Corynebacterium* sp., (b) (4) were interpreted with microbiological cut-off values suggested by EFSA guidance [2].

Table 2. Antimicrobial susceptibility of (b) (4) and KCCM 80346

Antibiotics	MIC ($mg \cdot L^{-1}$)		Interpretation[a]	
	(b) (4)	KCCM 80346	(b) (4)	KCCM 80346
Ampicillin	(b) (4)			
Vancomycin				
Gentamycin				
Kanamycin				
Streptomycin				
Erythromycin				
Clindamycin				
Tetracycline				
Chloramphenicol				

As shown in Table 2, the cell growth inhibition of production strain was observed in susceptible range. Therefore, it can be conclude that antimicrobial susceptibility by genetic modification is not occurred.



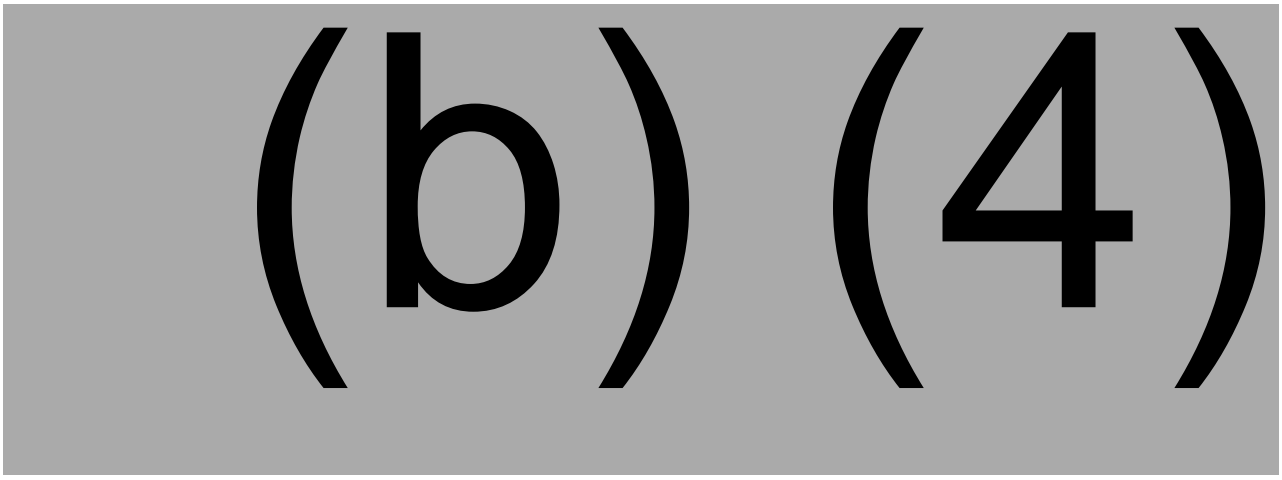
REFERENCES

[1] Clinical and Laboratory Standards Institute. 2012. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—9th ed. CLSI document M07-A9. Clinical and Laboratory Standards Institute, Wayne, PA

[2] EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2018. Guidance on the characterisation of microorganisms used as feed additives or as production. EFSA Journal, 16(3), 5206. DOI: 10.2903/j.efsa.2018.5206. Available online: https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2018.5206.

STUDY REPORT

Analysis of the absence of *Corynebacterium glutamicum* KCCM 80346 production strain from L-tryptophan fermentation product



Requested by
CJ Cheiljedang Corp.
55, Gwanggyo-ro 42-gil,
Yeongtong-gu, Suwon-si,
Gyeonggi-do,
Republic of Korea

This report contains scientific interpretation of the received data by the named scientists in the (b) (4) It does not necessarily represent the official views of the competent authorities.

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NOTE
The samples will be stored for three months after reporting the results.
Copies of all the laboratory data are available to the client on request.

EXECUTIVE SUMMARY

Scope

CJ Cheiljedang Corp. requested (b) (4) to analyse the absence of the production strain *Corynebacterium glutamicum* KCCM 80346 in the L-tryptophan product in compliance with the EFSA FEEDAP Panel (2018) Guidance on the characterisation of microorganisms used as feed additives or as production organisms, Section 3.1. Absence of the production strain.

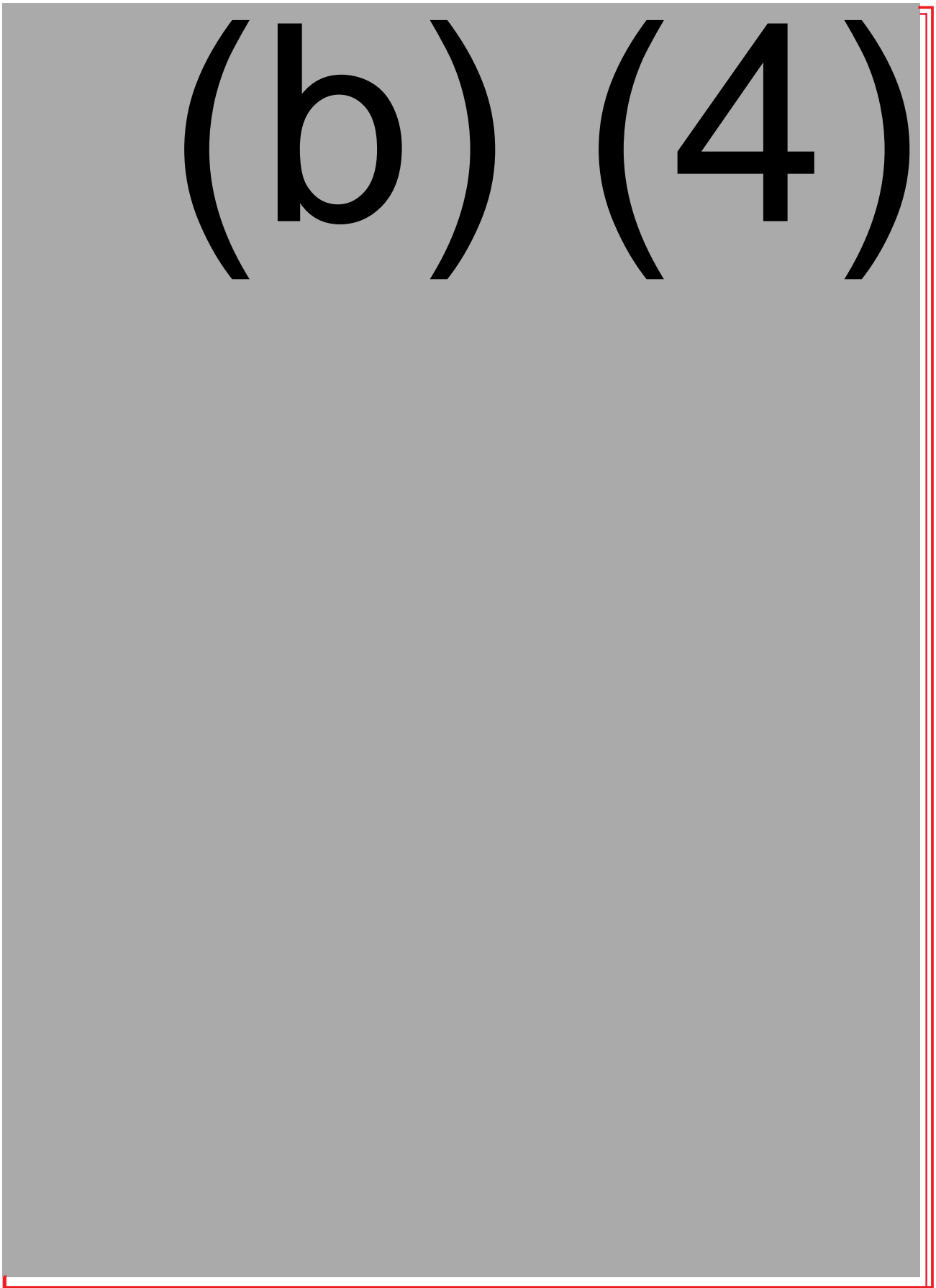
Strategy

The test was performed according to the European Food Safety Authority (EFSA) FEEDAP Panel (2018) Guidance, Section 3.1 (Absence of the production strain). (b) (4)

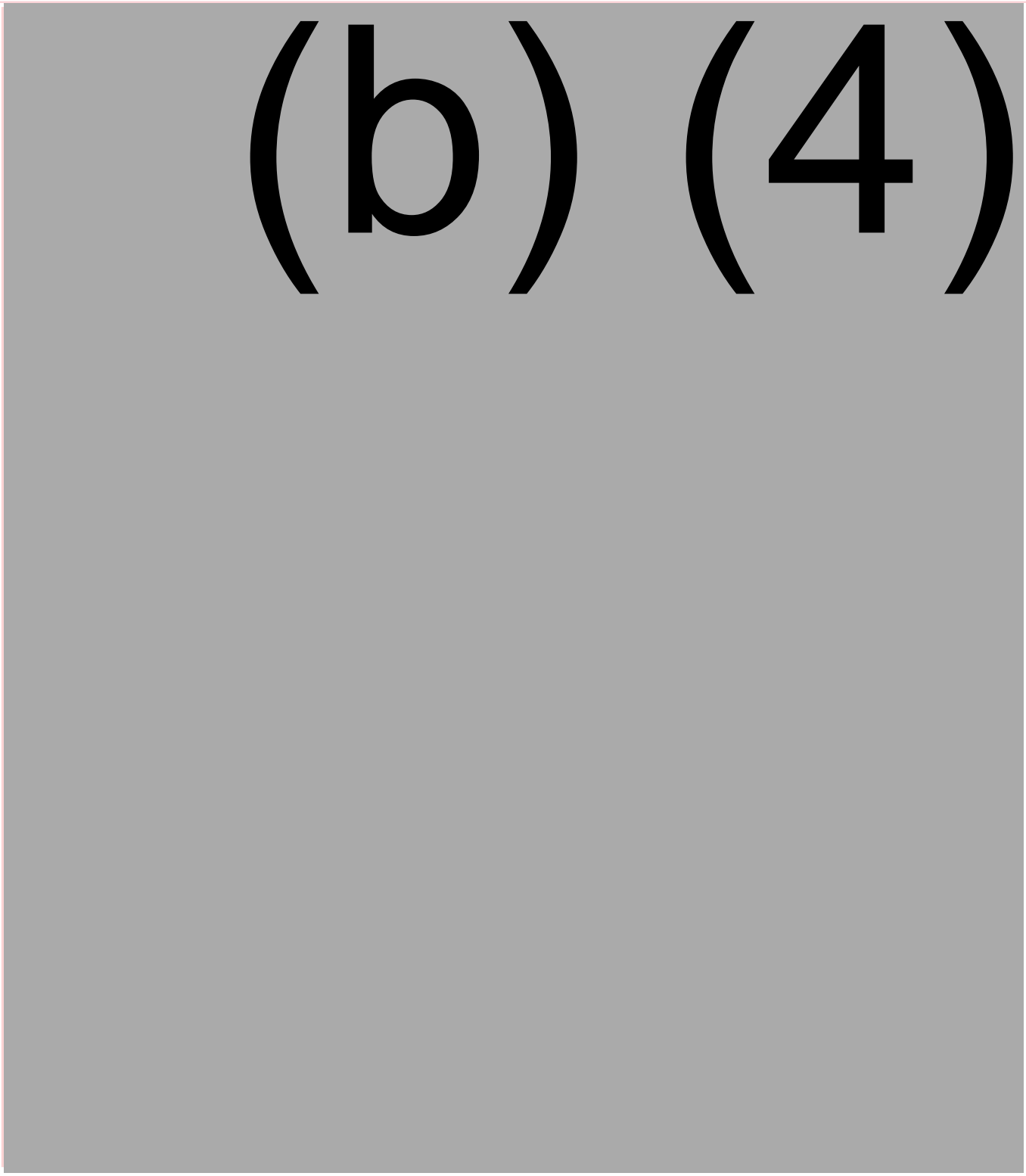
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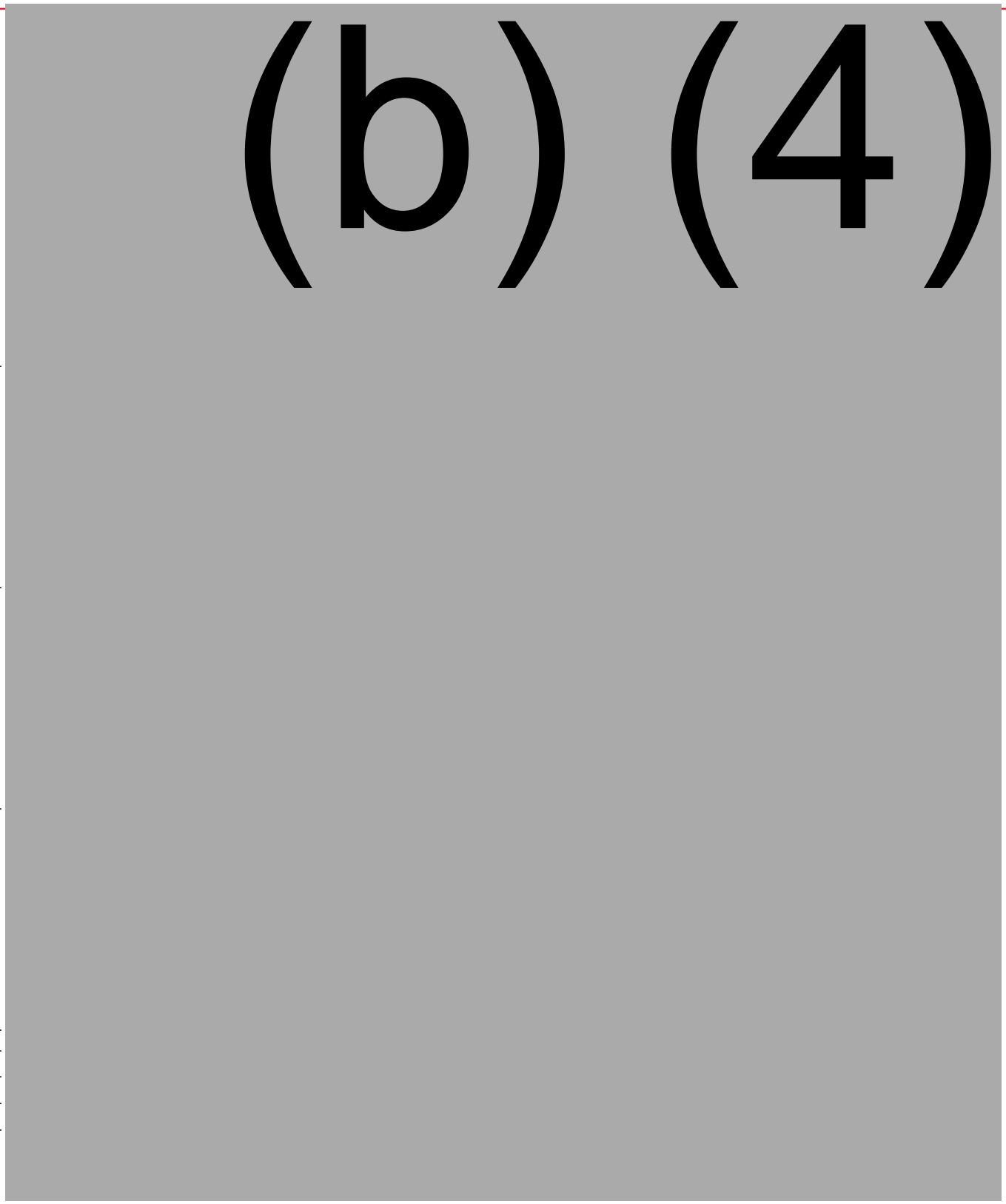
Results

(b) (4)

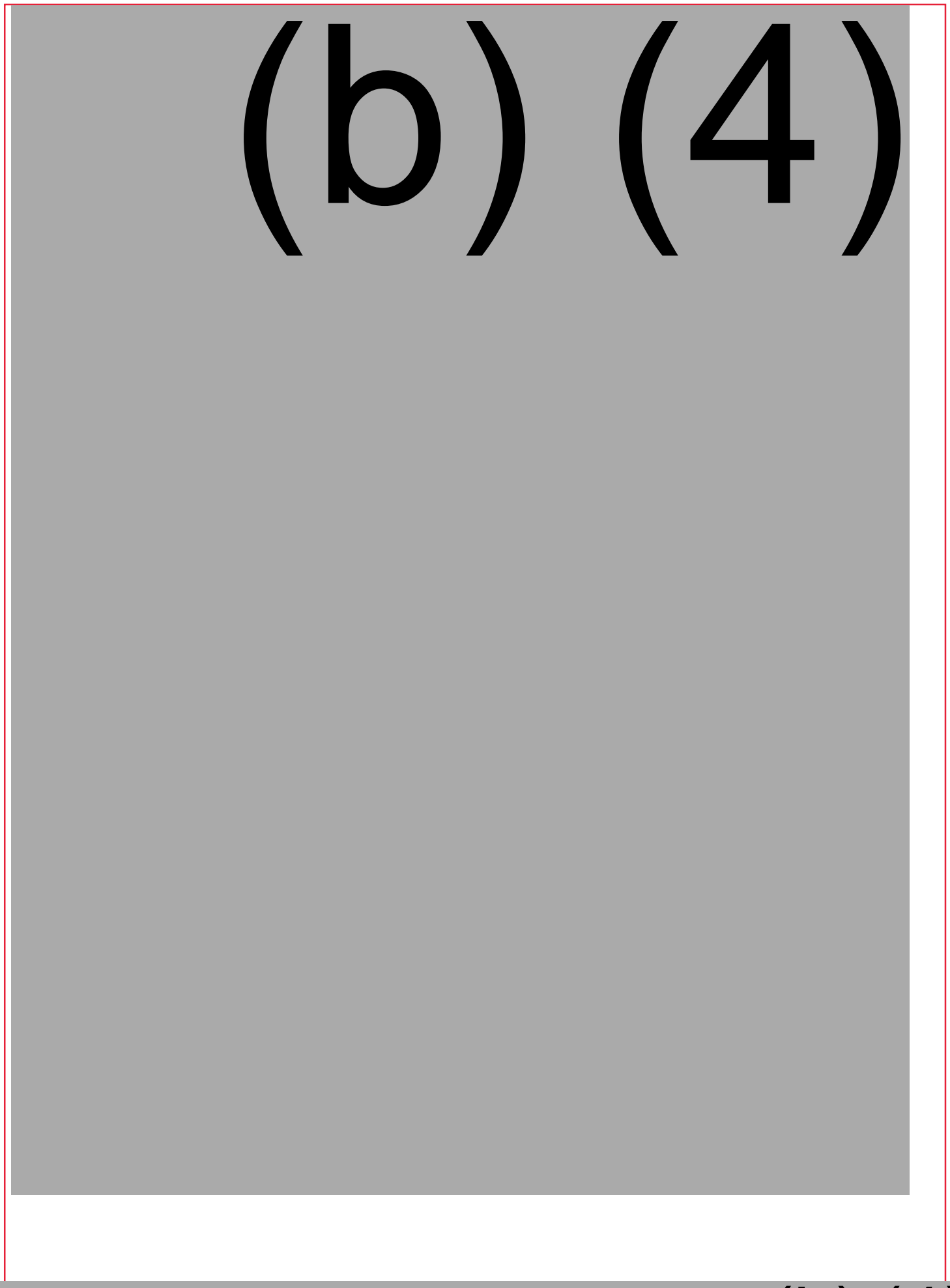


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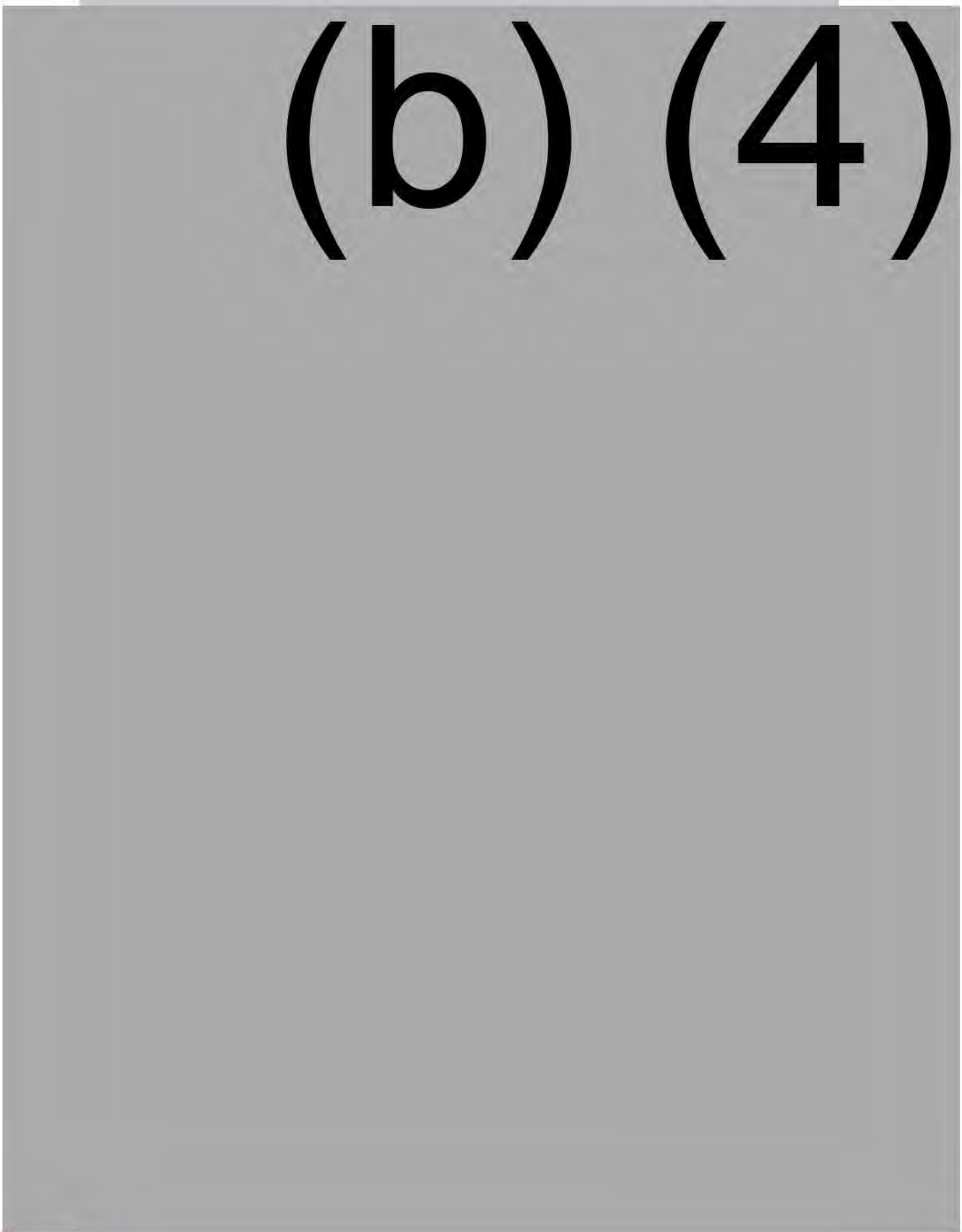

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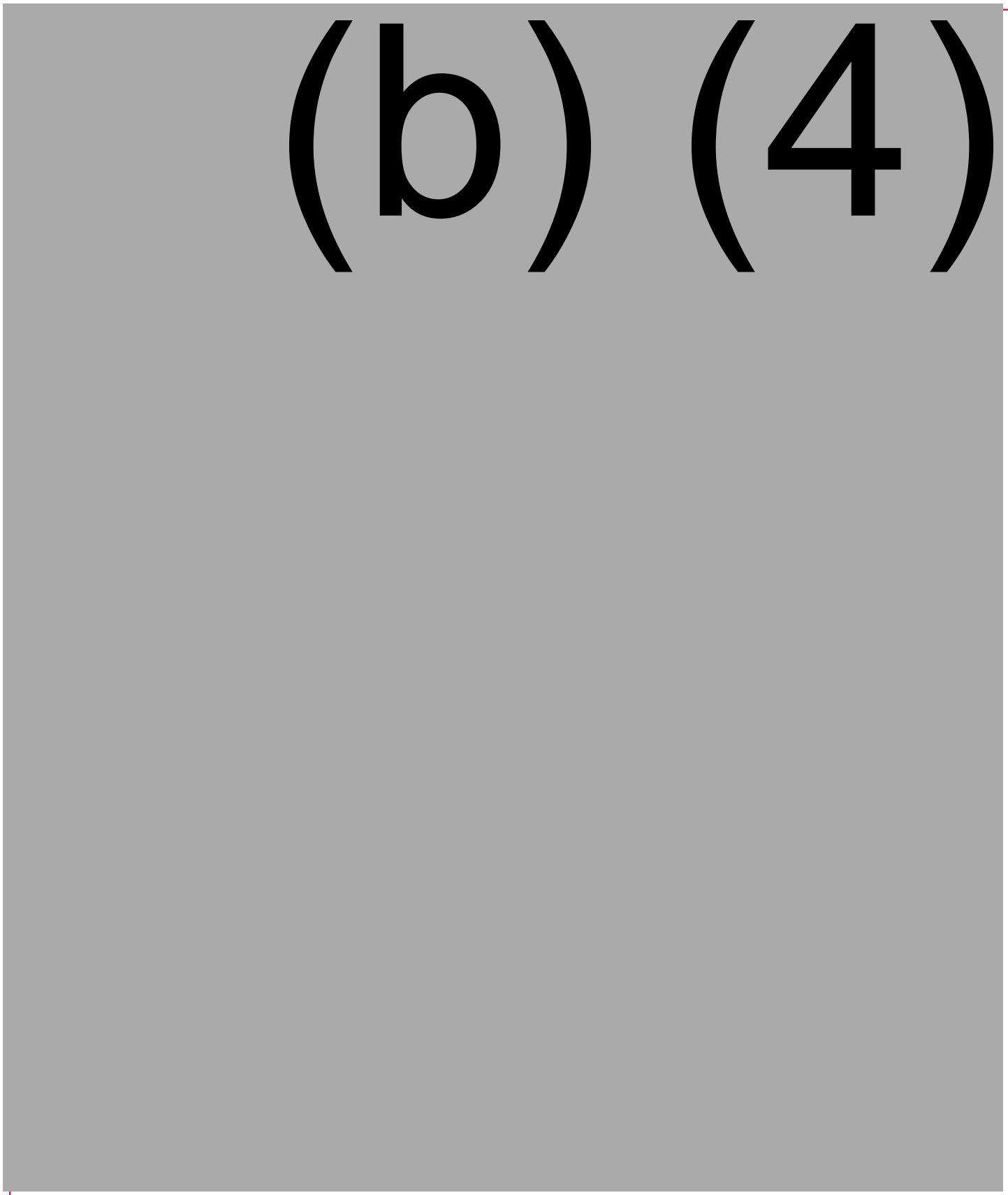
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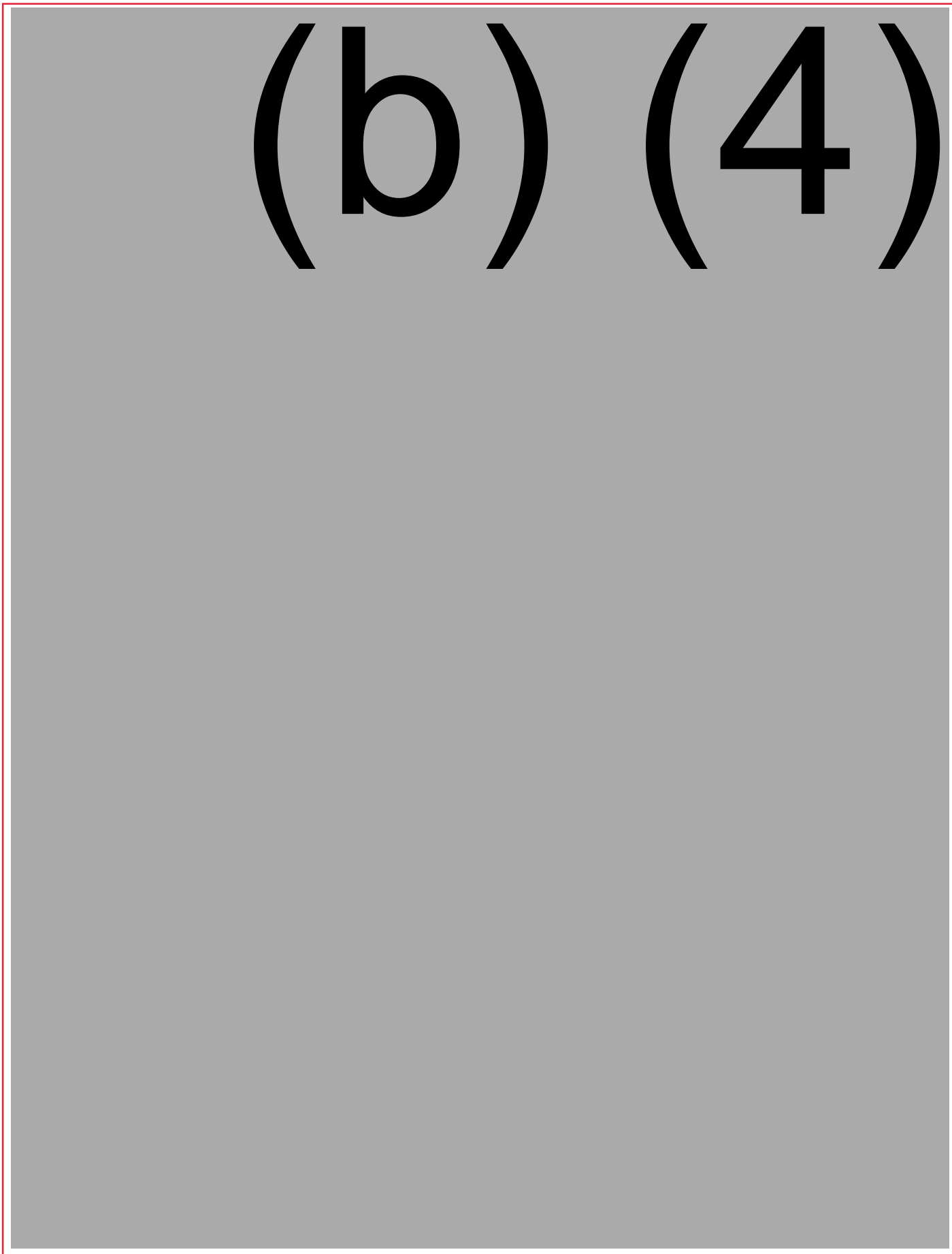
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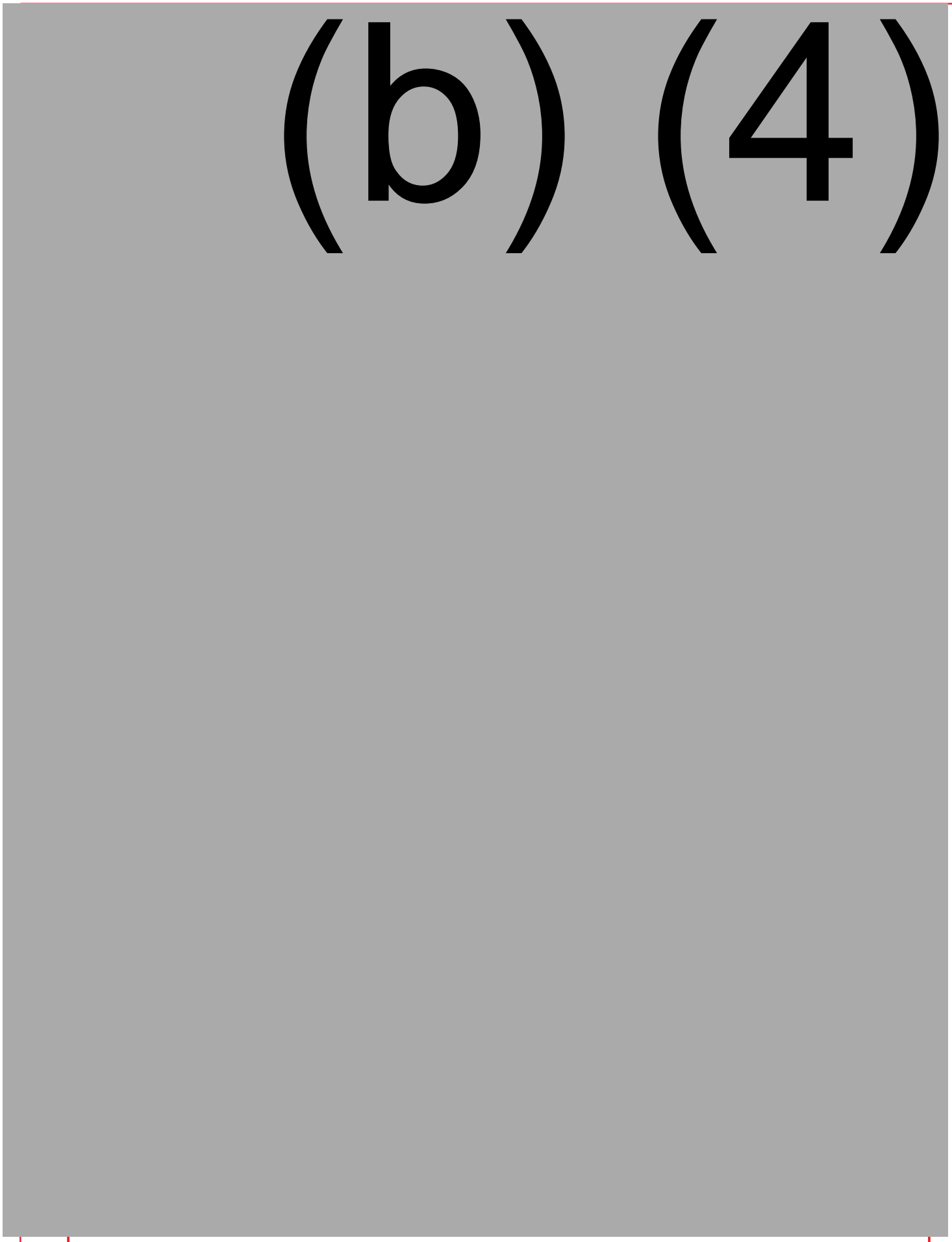
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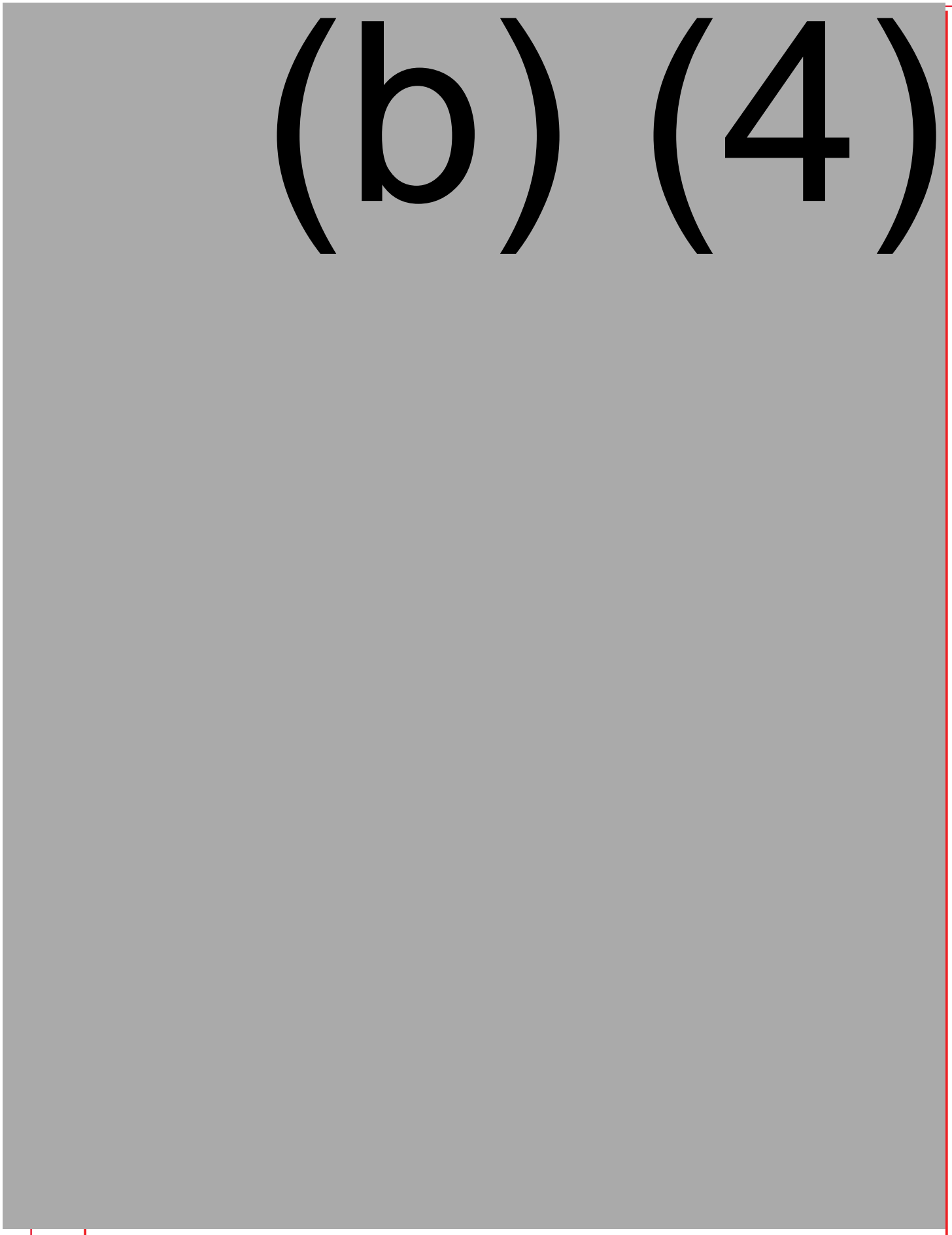
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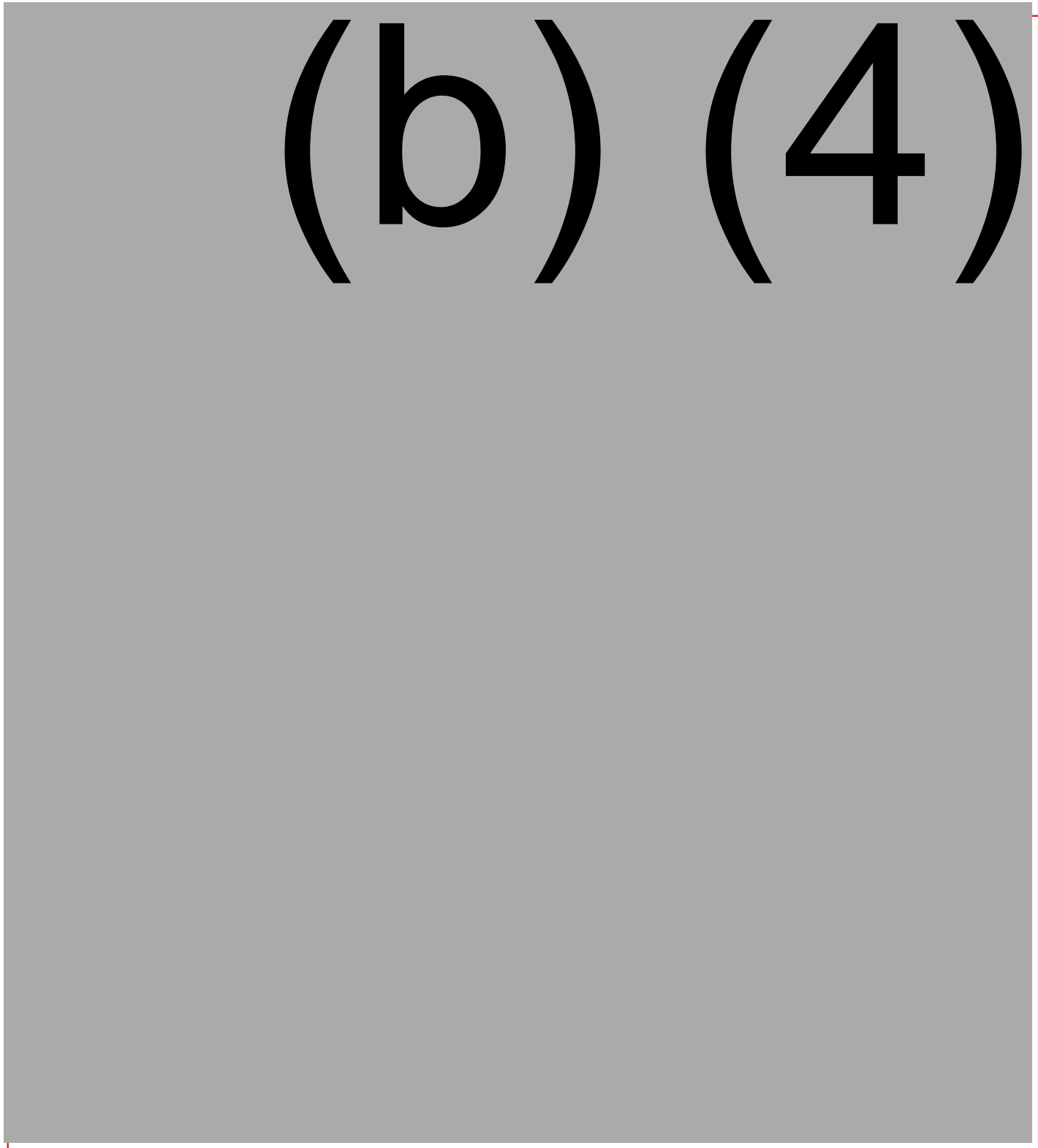
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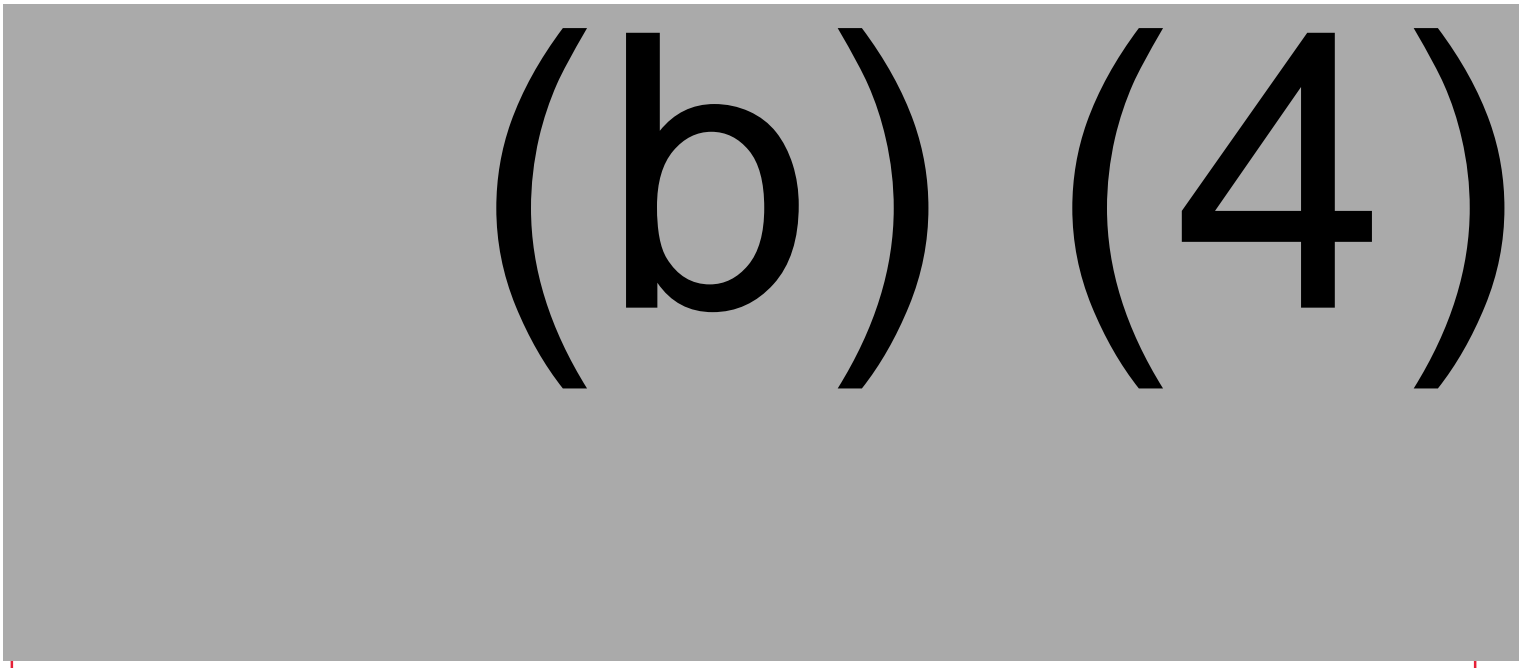
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CONFIDENTIAL REPORT

Genetic Stability of *C. glutamicum* KCCM 80346

Version 1.0

TITLE

Genetic stability of *C. glutamicum* KCCM 80346

OBJECTIVE OF THE STUDY

This study was conducted to examine the genetic stability of L-tryptophan production strain, *C. glutamicum* KCCM 80346

SCHEDULE OF THE STUDY

Initiation of experiment: August 18, 2021

Termination of experiment: August 26, 2021

Submission of final report: August 31, 2021

TESTING FACILITY

R&BD)Regulatory Affairs, CJ CheilJedang
55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do 16495, Korea

RESPONSIBLE STAFFS

Analyst and Author

(b)(6)

Report approved by

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MATERIAL AND METHODS 5

Test Samples 5

PCR Analysis 5

RESULTS 7

INTRODUCTION

Corynebacterium glutamicum KCCM 80346 is a genetically modified strain for Dried L-Tryptophan Fermentation Product production. Among the genetically modified region, *trp*A gene from *Escherichia coli* was chosen to confirm a genetic stability of production strain through whole fermentation process.

In this study, the genetic stability of *C. glutamicum* KCCM 80346 was confirmed by detecting specifically modified gene with PCR analysis. To verify the genetic stability of production strain, the maintenance of (b) (4) on the chromosome was observed during the fermentation.

MATERIAL AND METHODS

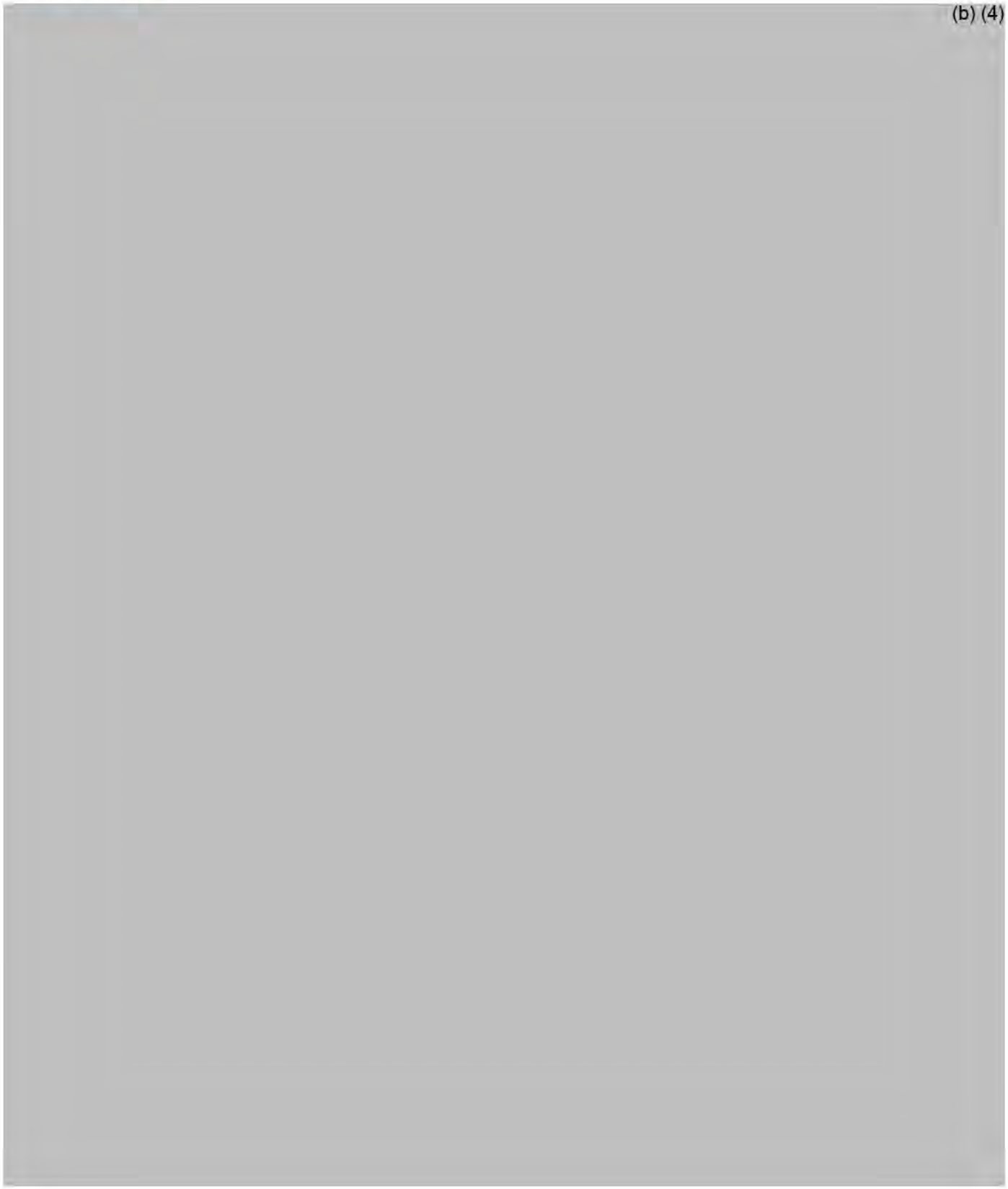
Test Samples

(b) (4)


(b) (4)

RESULTS

(b) (4)



CONFIDENTIAL REPORT

Whole genome sequence analysis of

Corynebacterium glutamicum KCCM 80346

Version 2.0

TITLE

Whole genome sequence analysis of *Corynebacterium glutamicum* KCCM 80346

OBJECTIVE OF THE STUDY

This study was conducted to analyse the genomic features of production strain, *Corynebacterium glutamicum* KCCM 80346.

SCHEDULE OF THE STUDY

Initiation of experiment: 03 August 2021

Termination of experiment: 29 October 2021

Submission of final report: 08 November 2021

Revision of final report: 18 July 2023

TESTING FACILITY

Digital&Technology, R&D, BIO, CJ CheilJedang
55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do 16495, Korea

RESPONSIBLE STAFFS

Analyst	(b)(6)
Author	
Report approved by	

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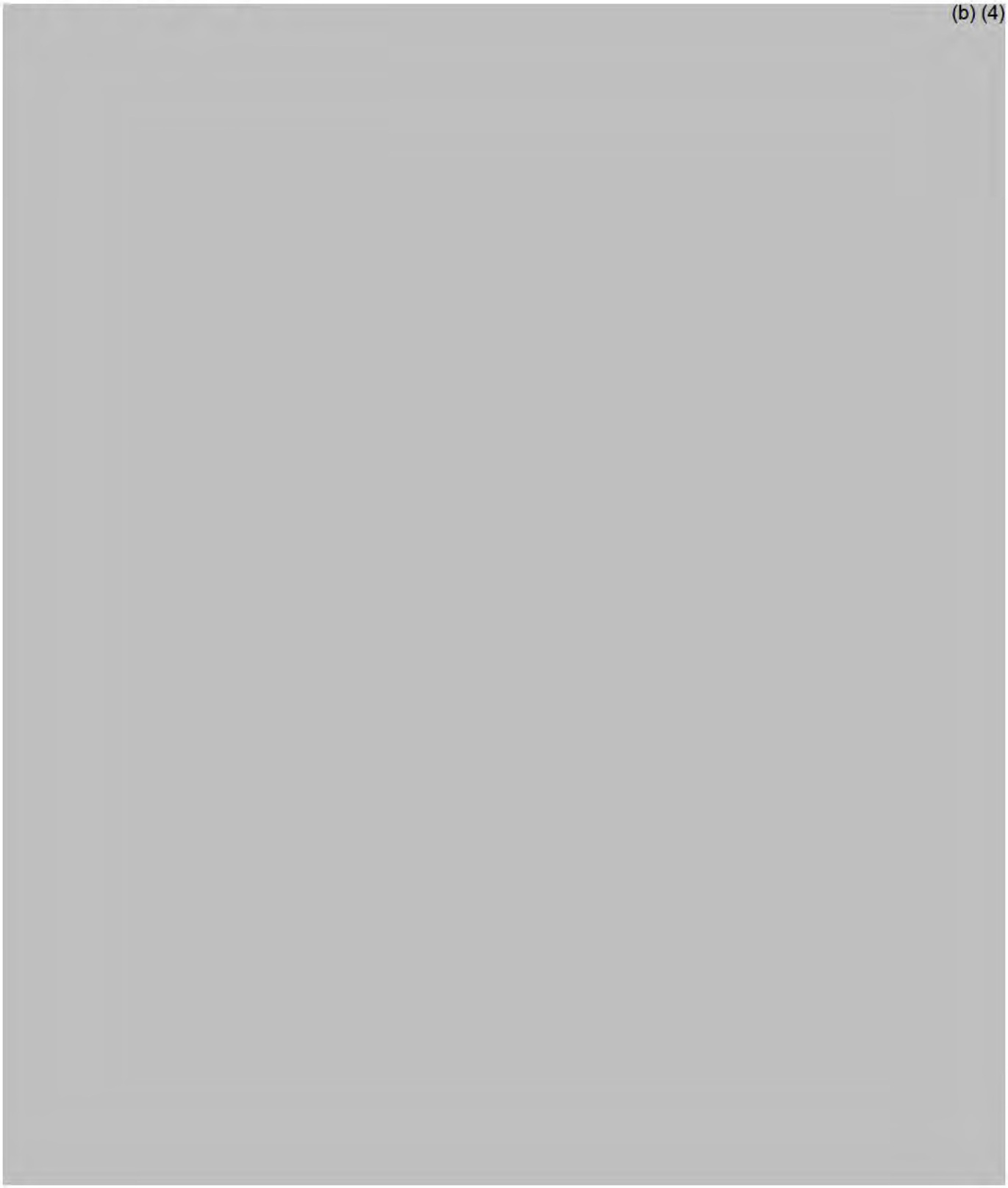
INTRODUCTION

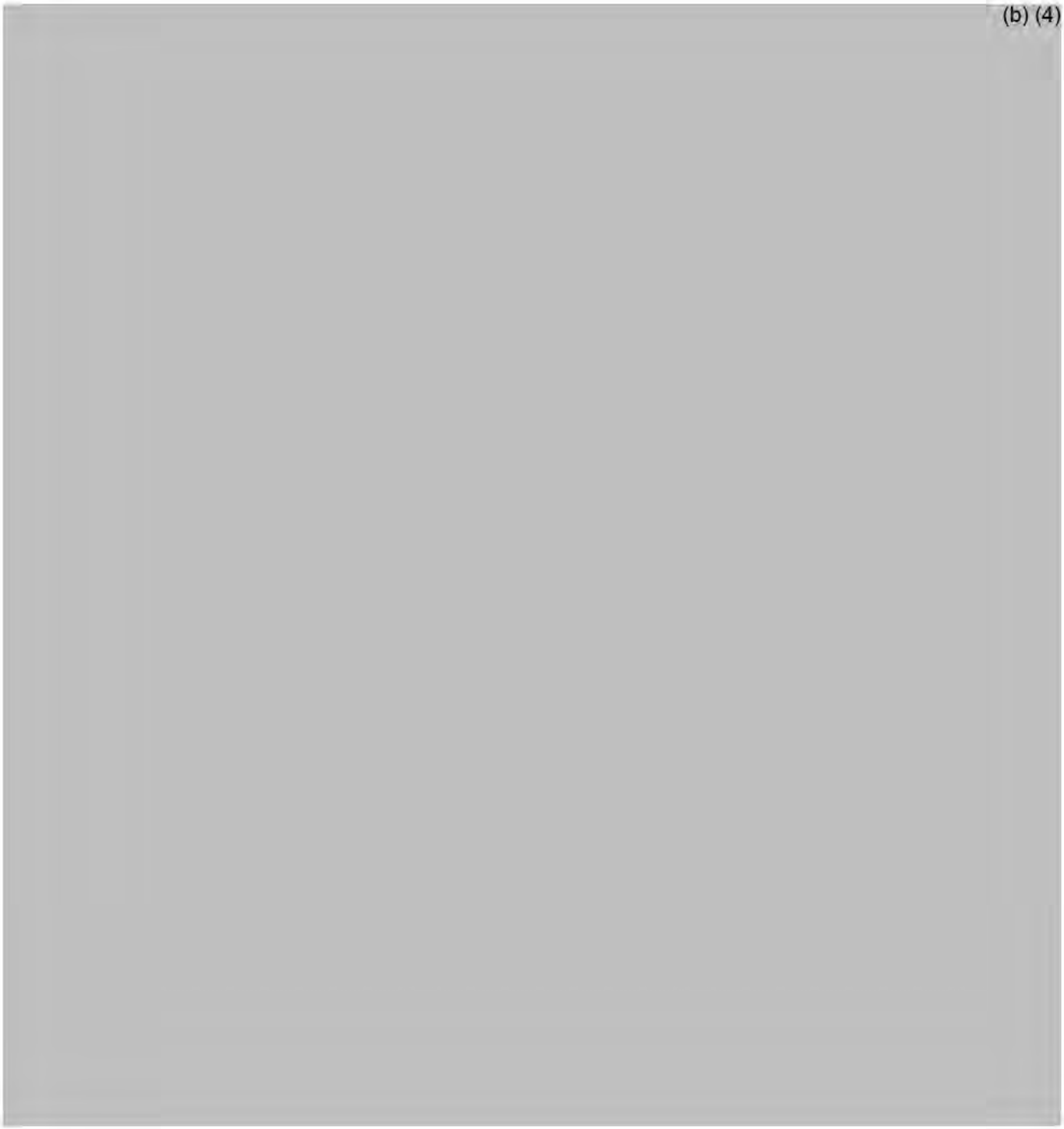
L-Tryptophan is produced by fermentation with *Corynebacterium glutamicum* KCCM 80346. The genome sequence analysis of the production strains should be performed for safety aspects. This study provides the information about the analysis method and WGS-based characterization of the production strain, *C. glutamicum* KCCM 80346.

MATERIALS AND METHODS

1. Genome sequencing

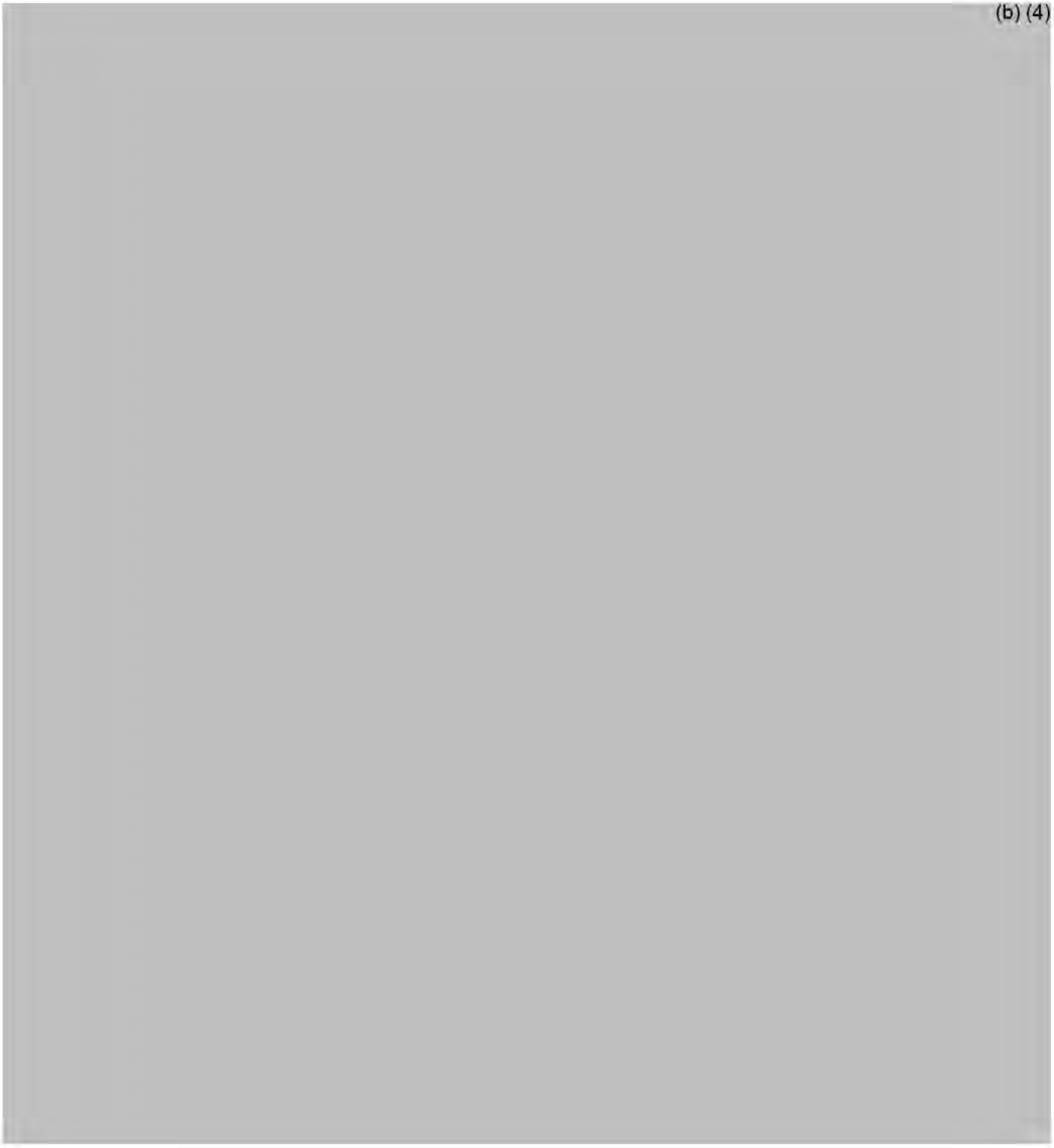
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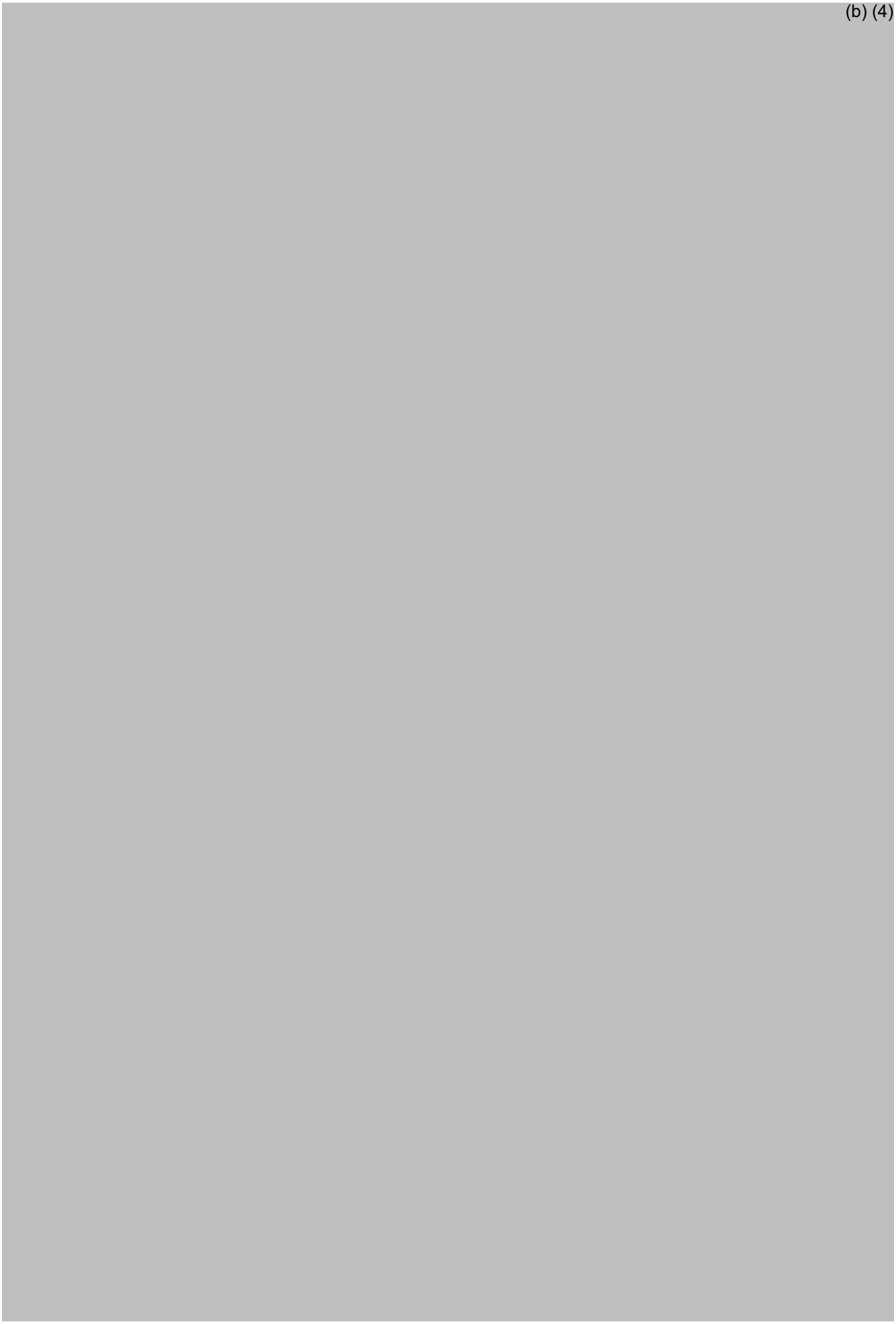


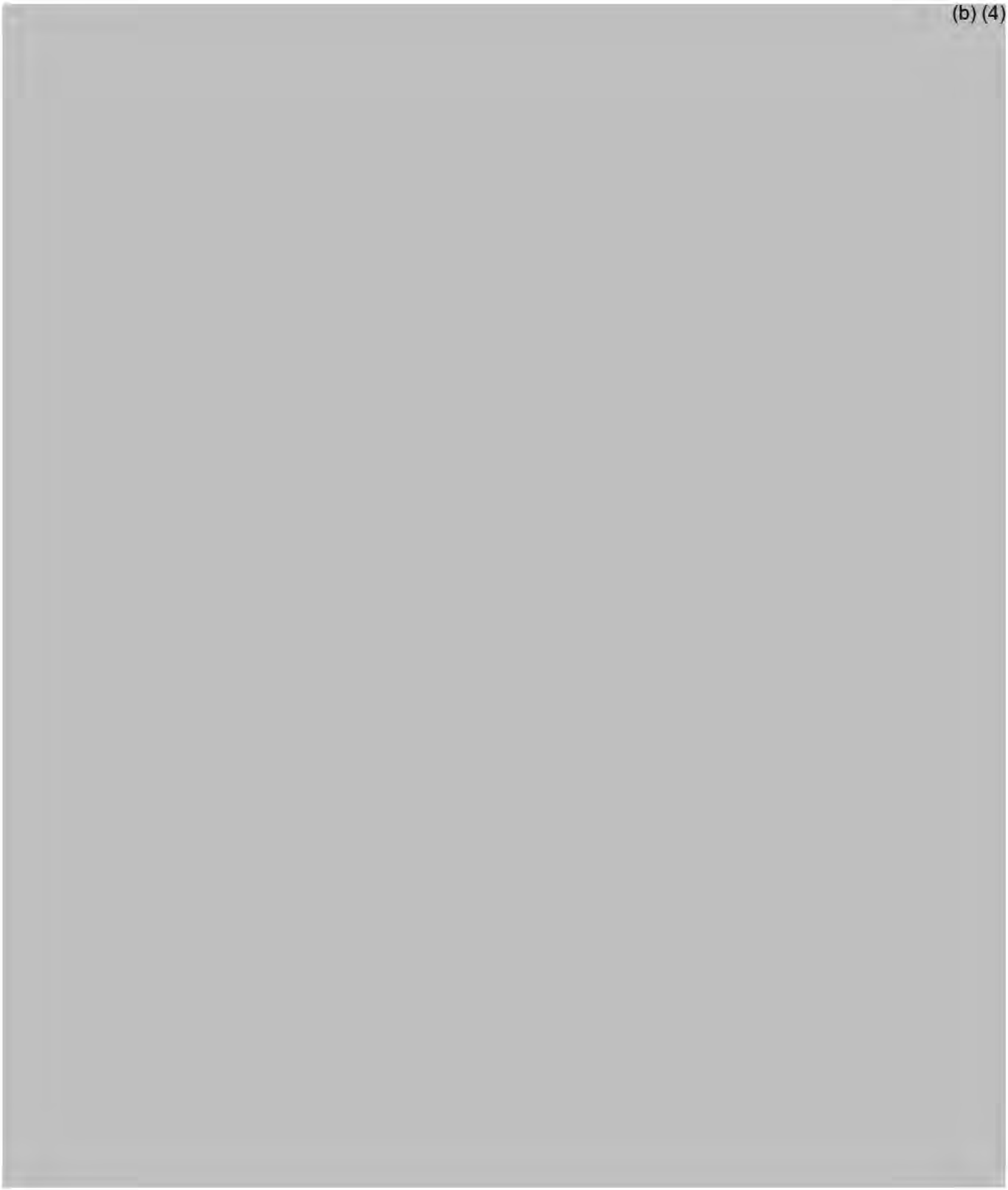

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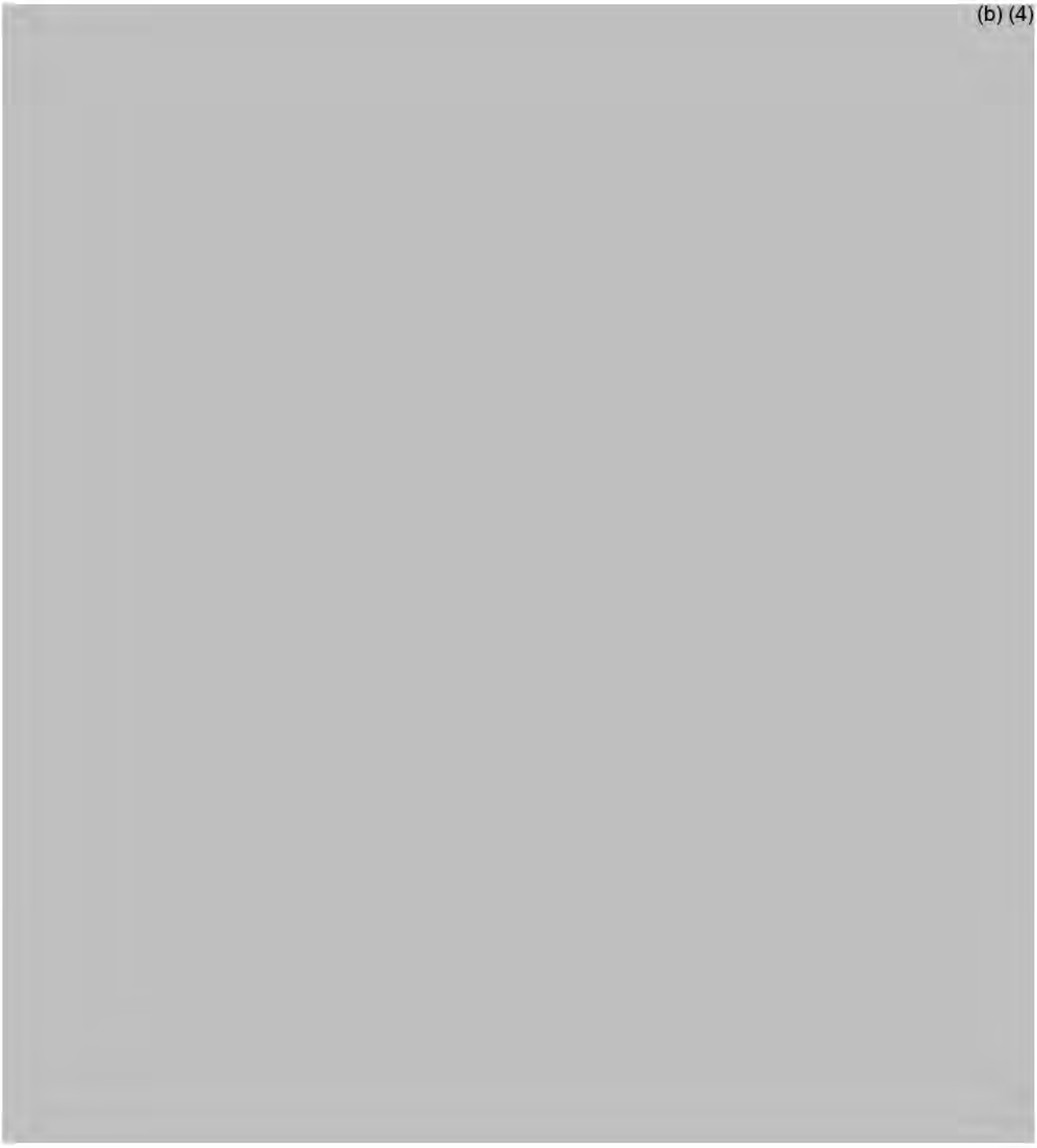
RESULTS

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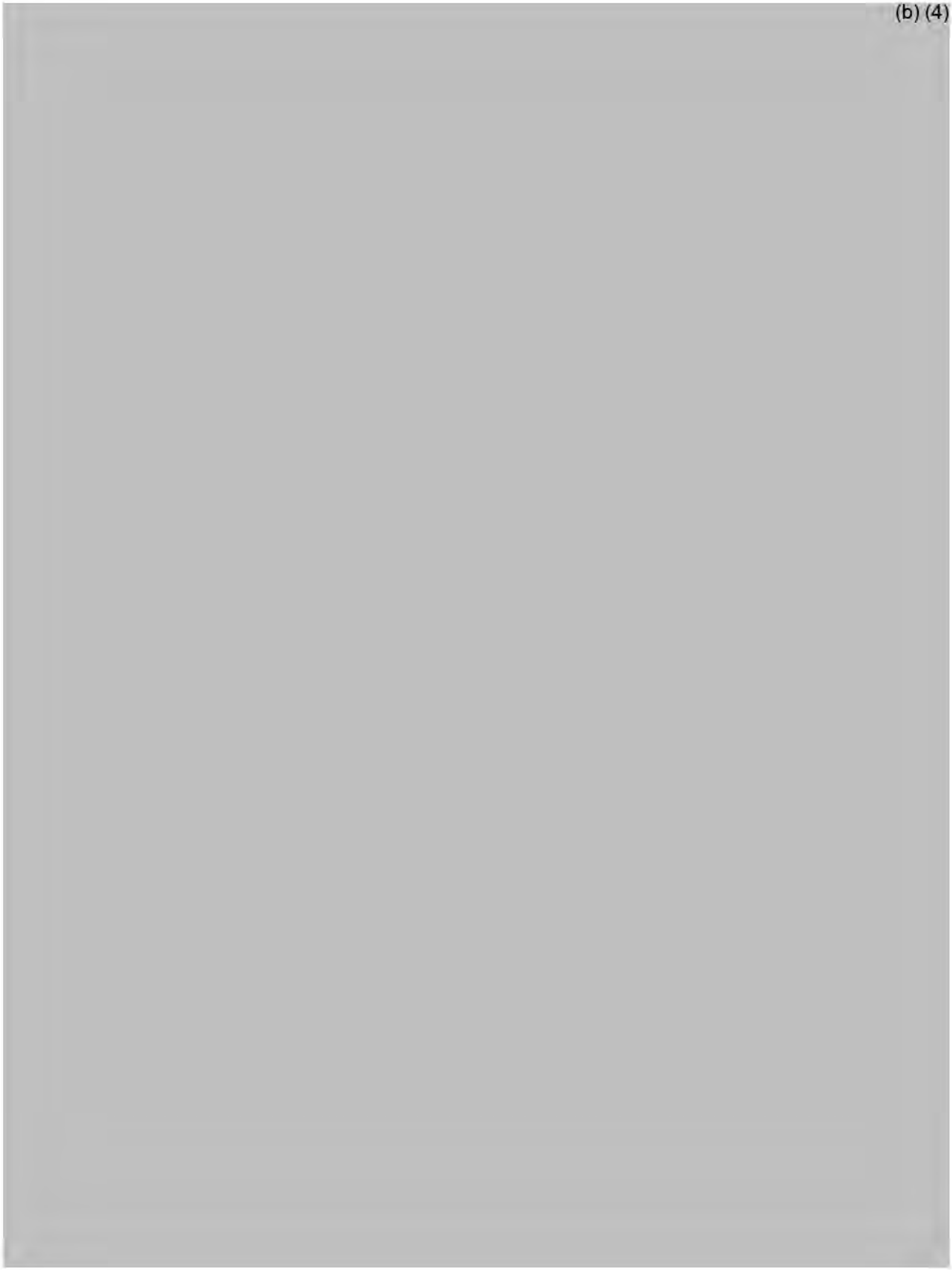

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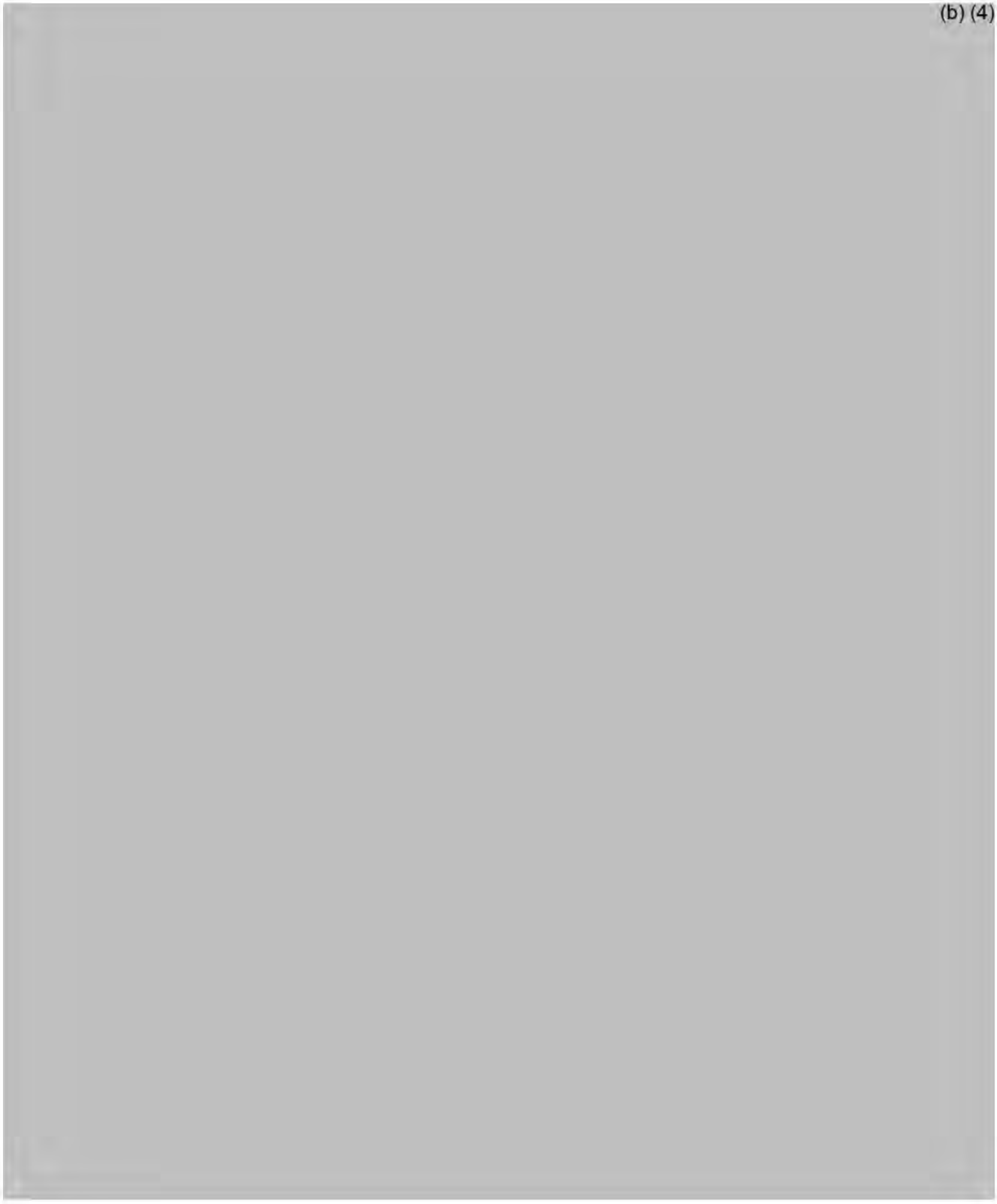

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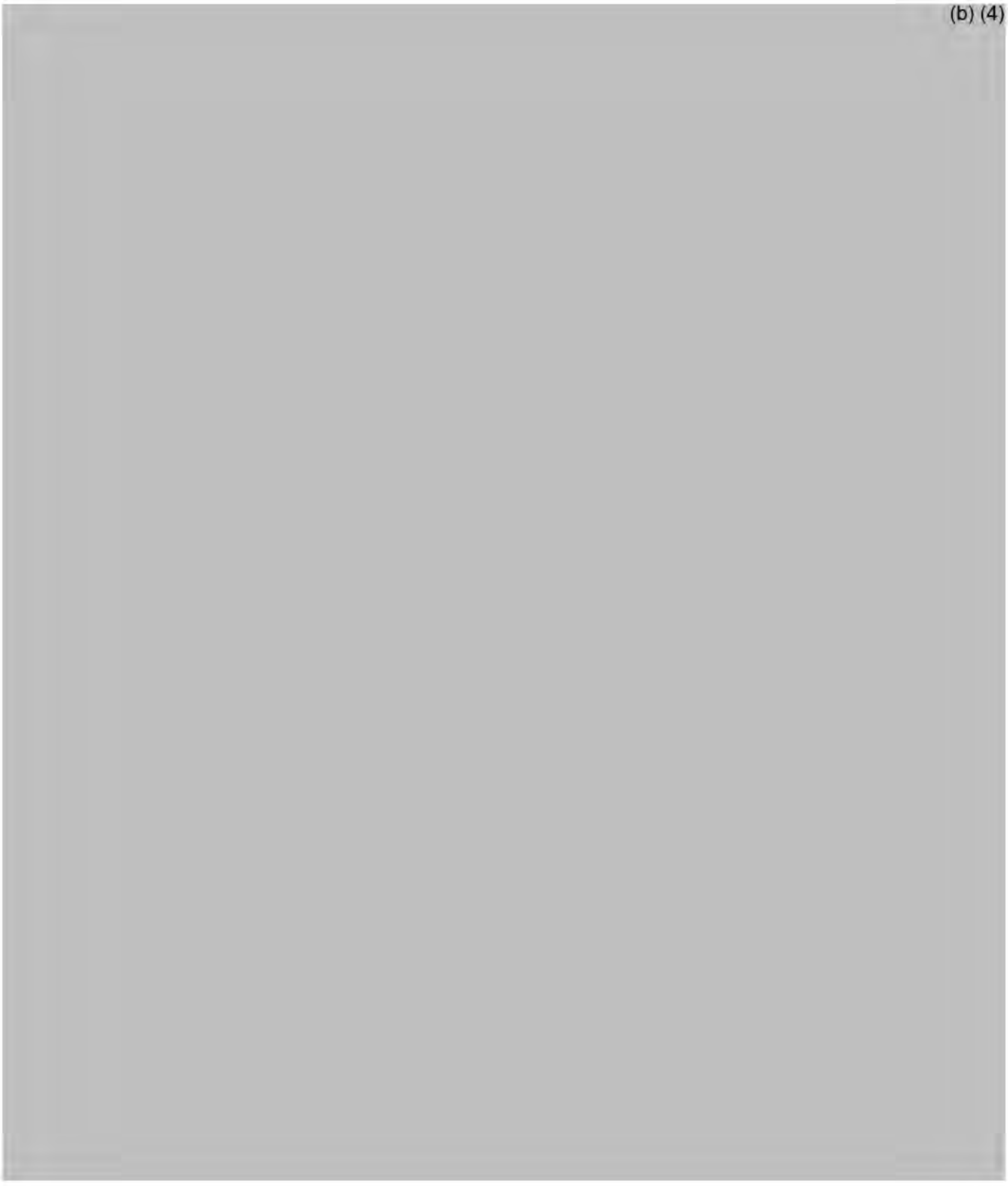

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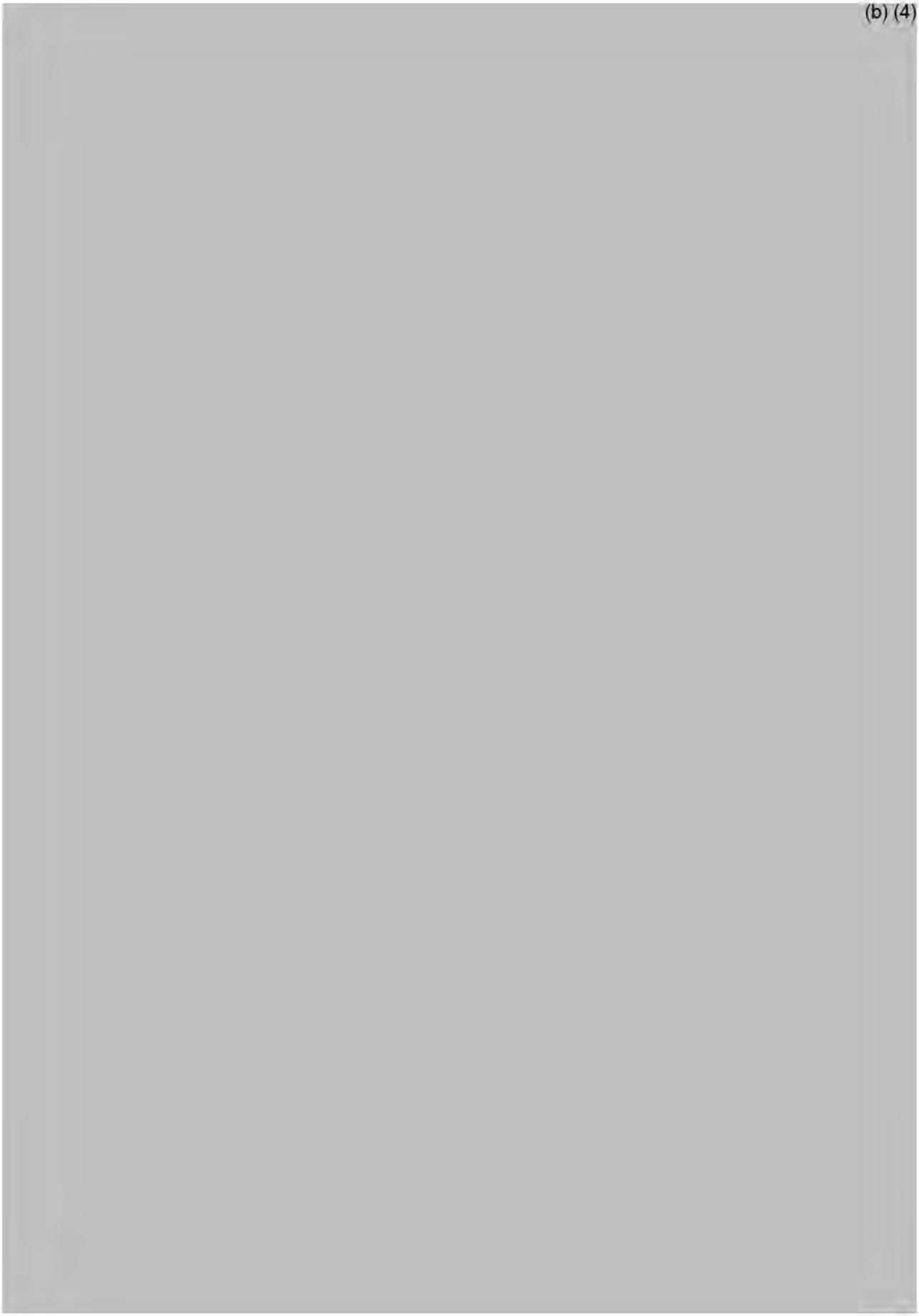

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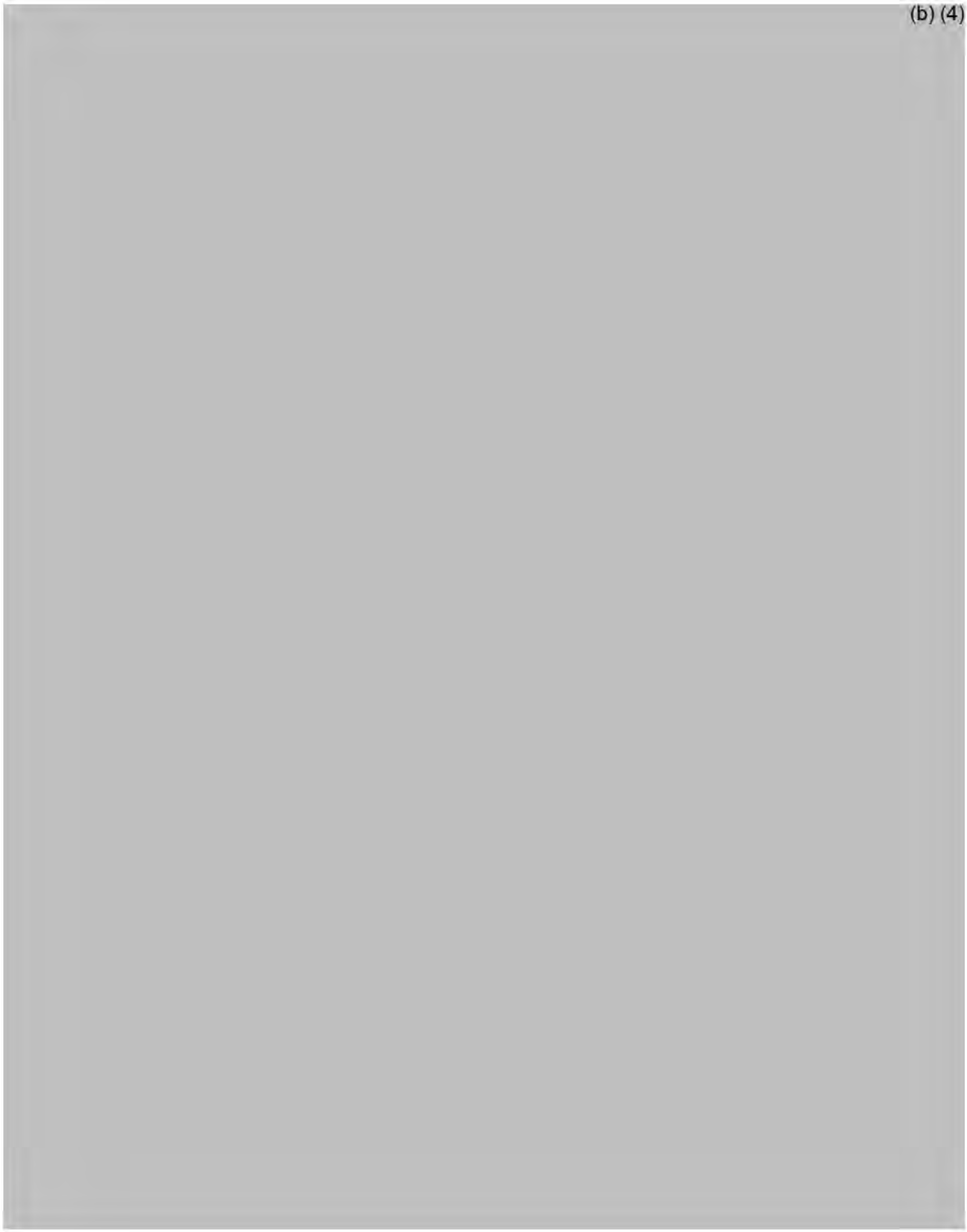

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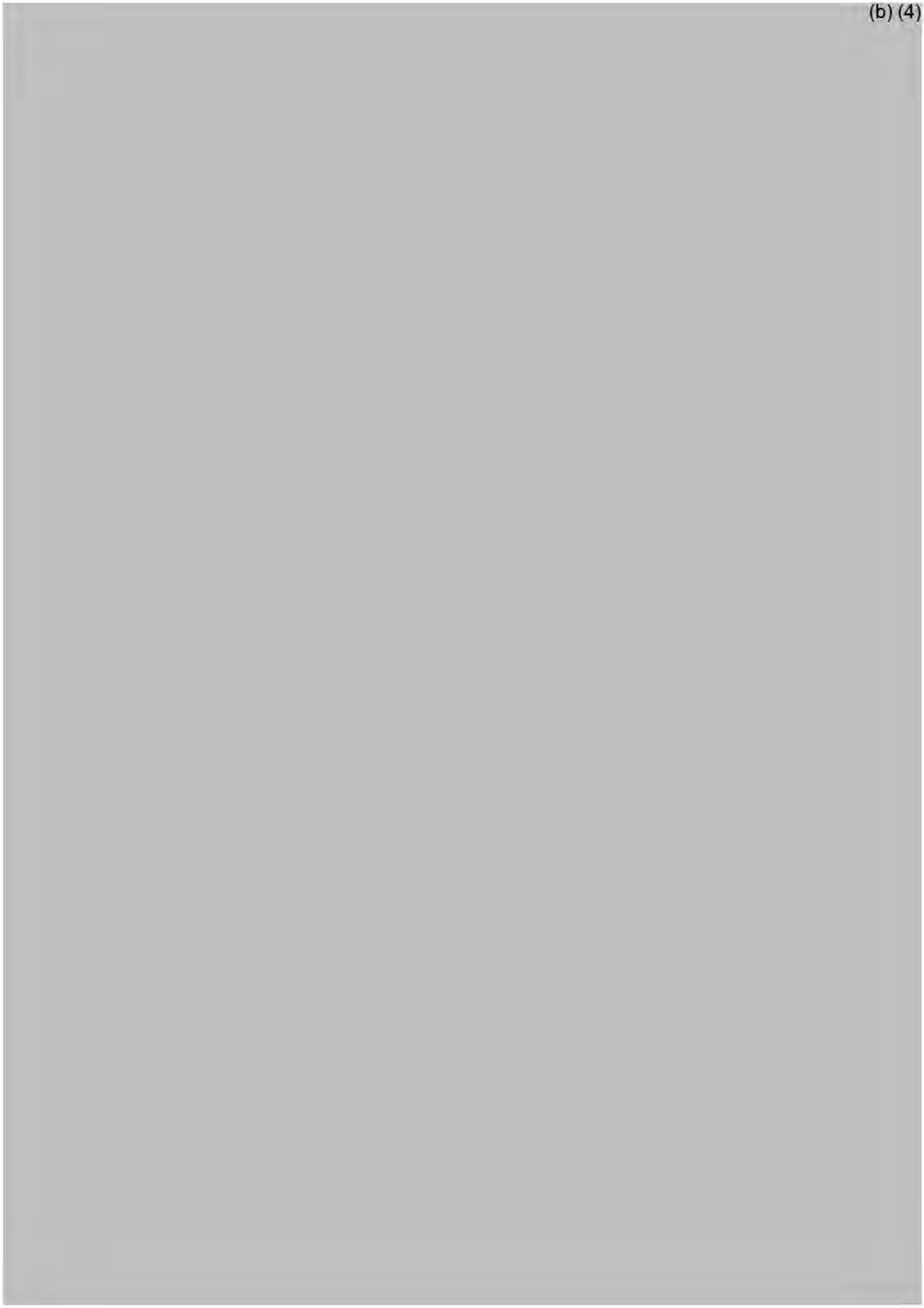

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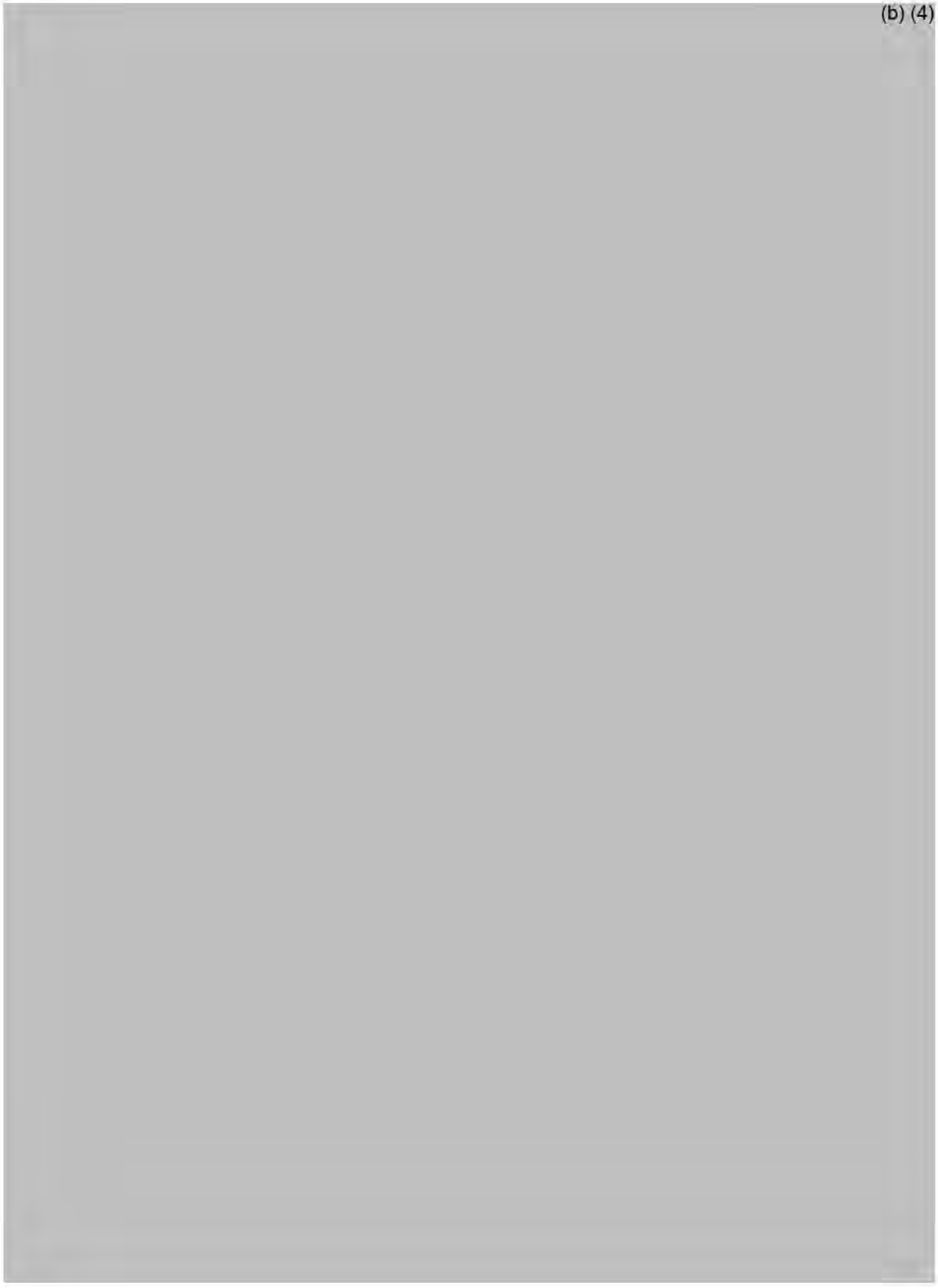

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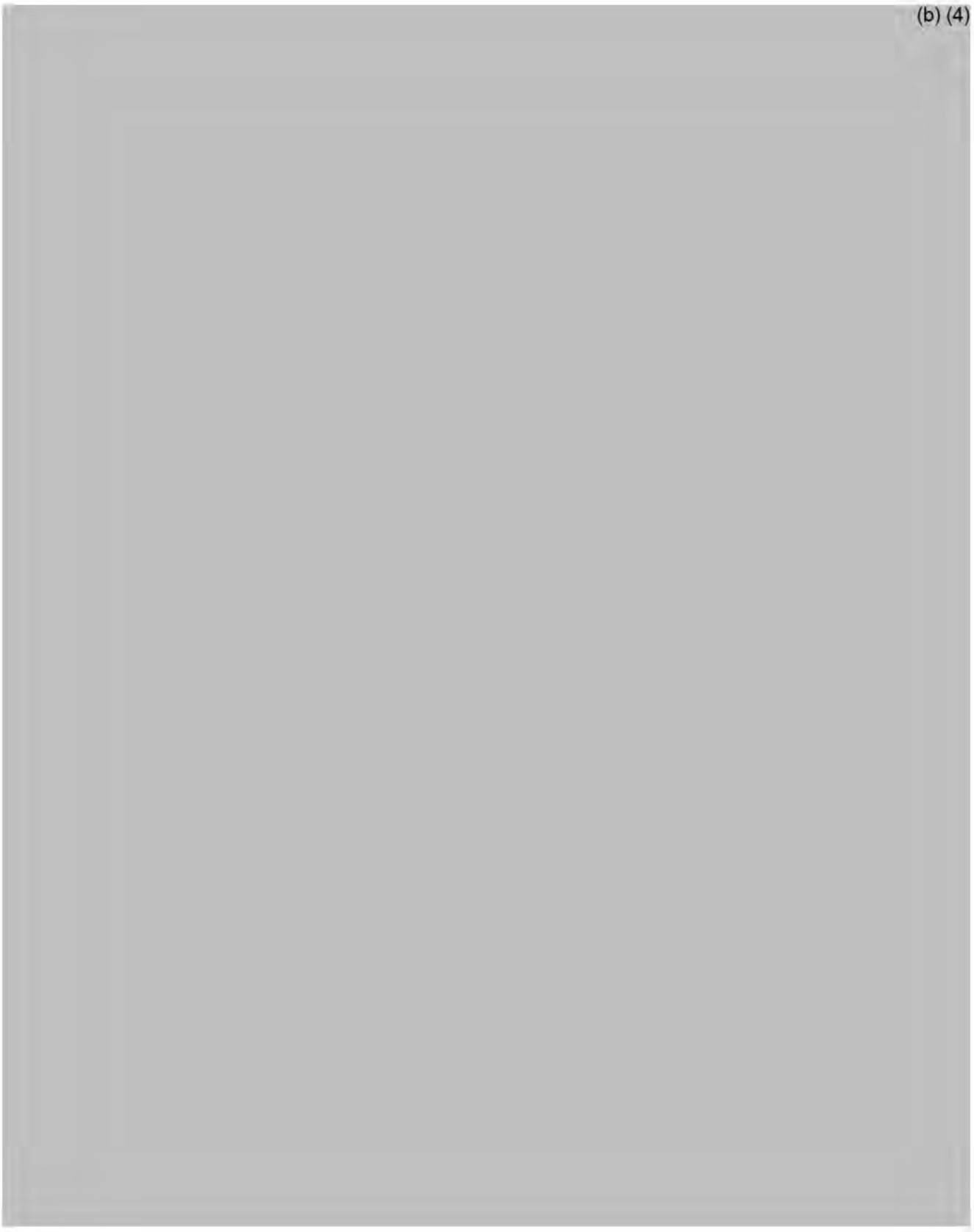

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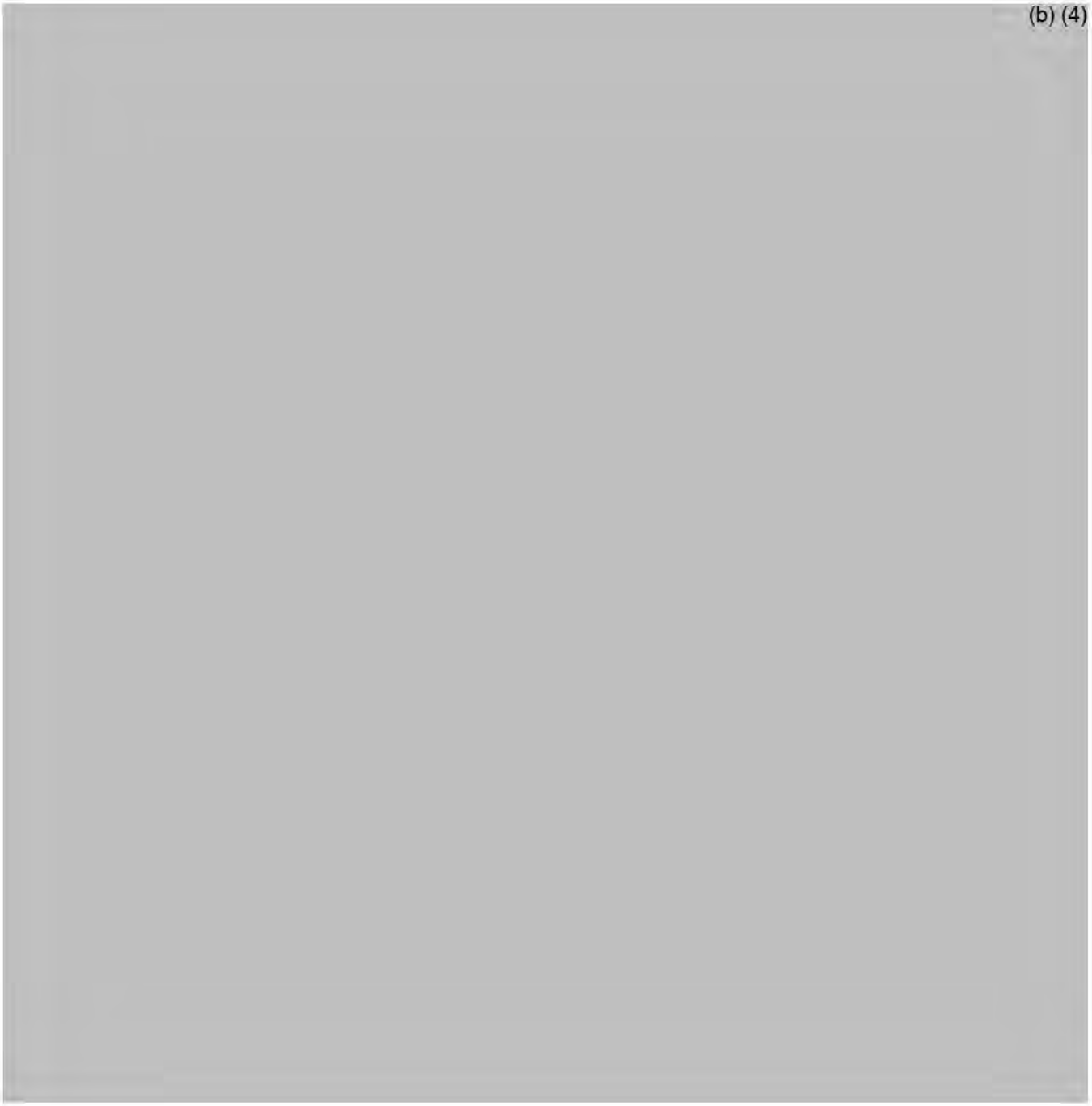
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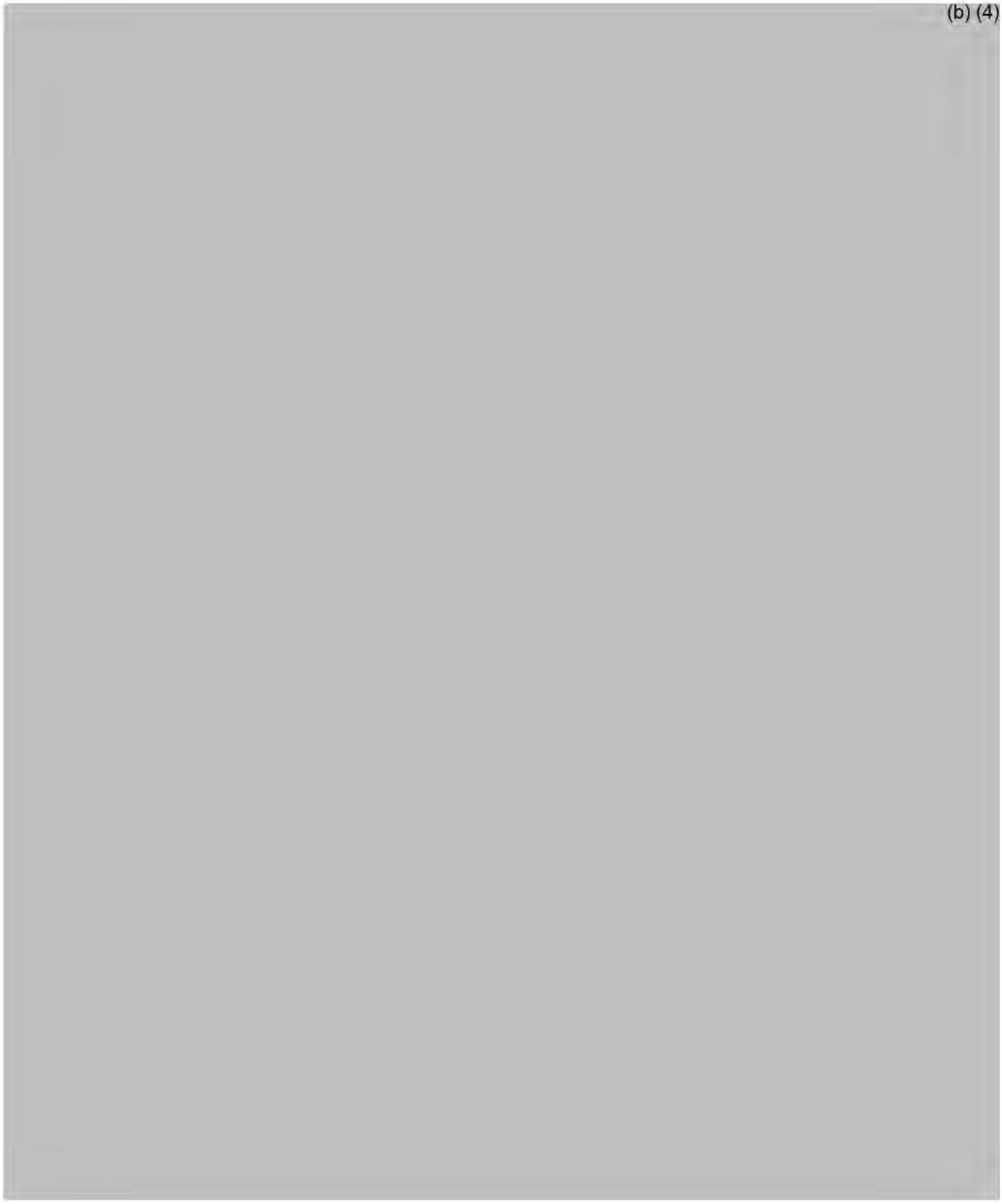

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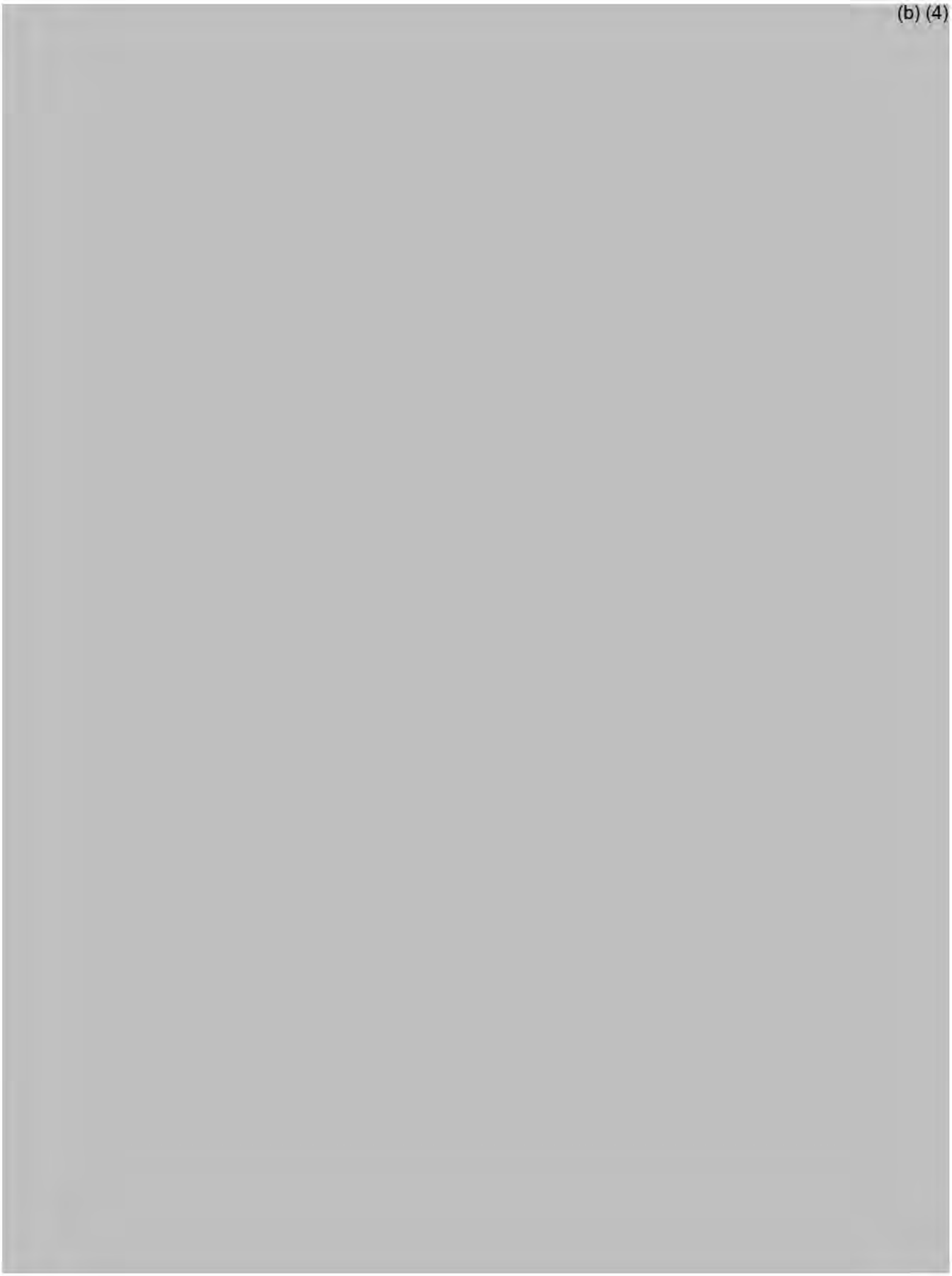


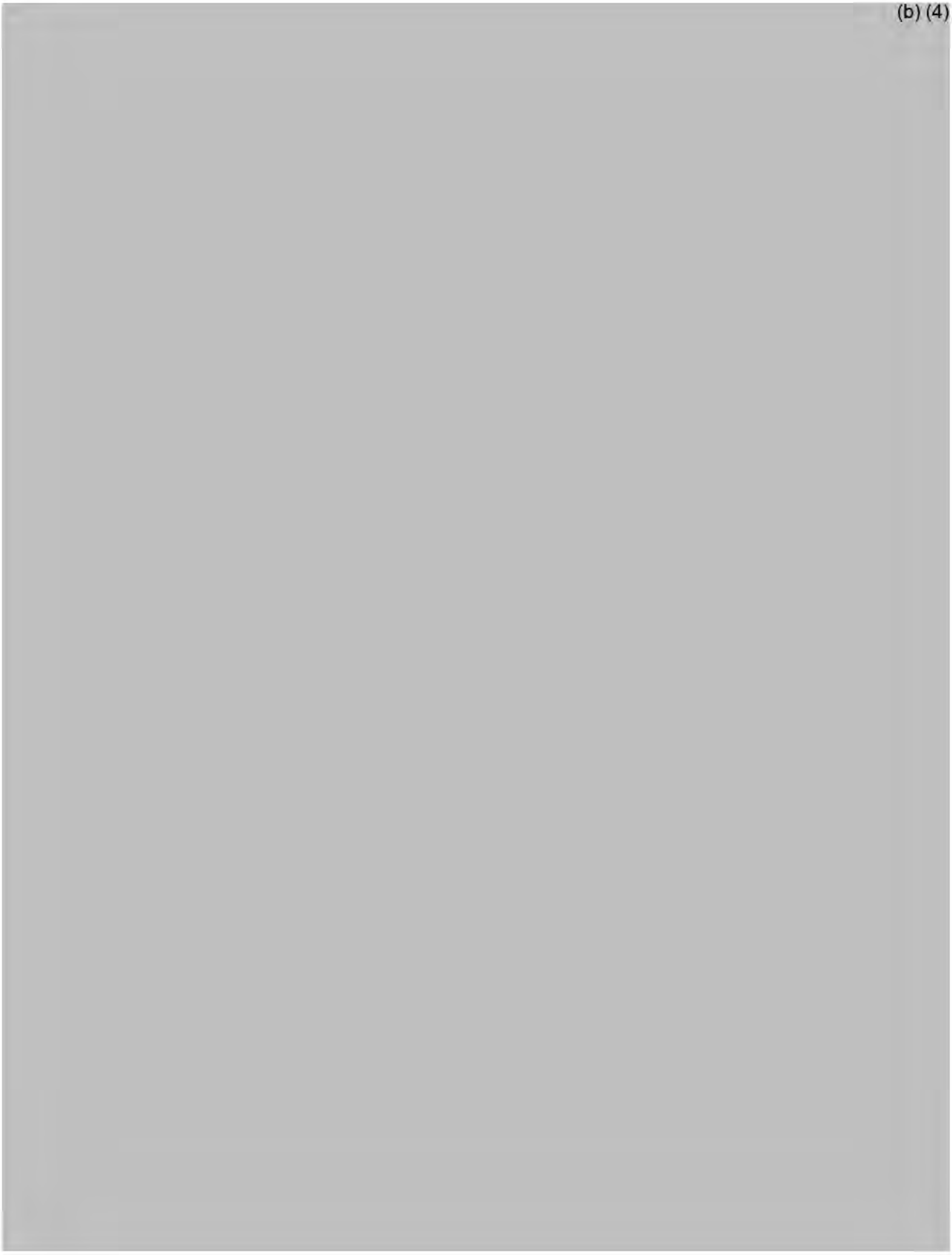


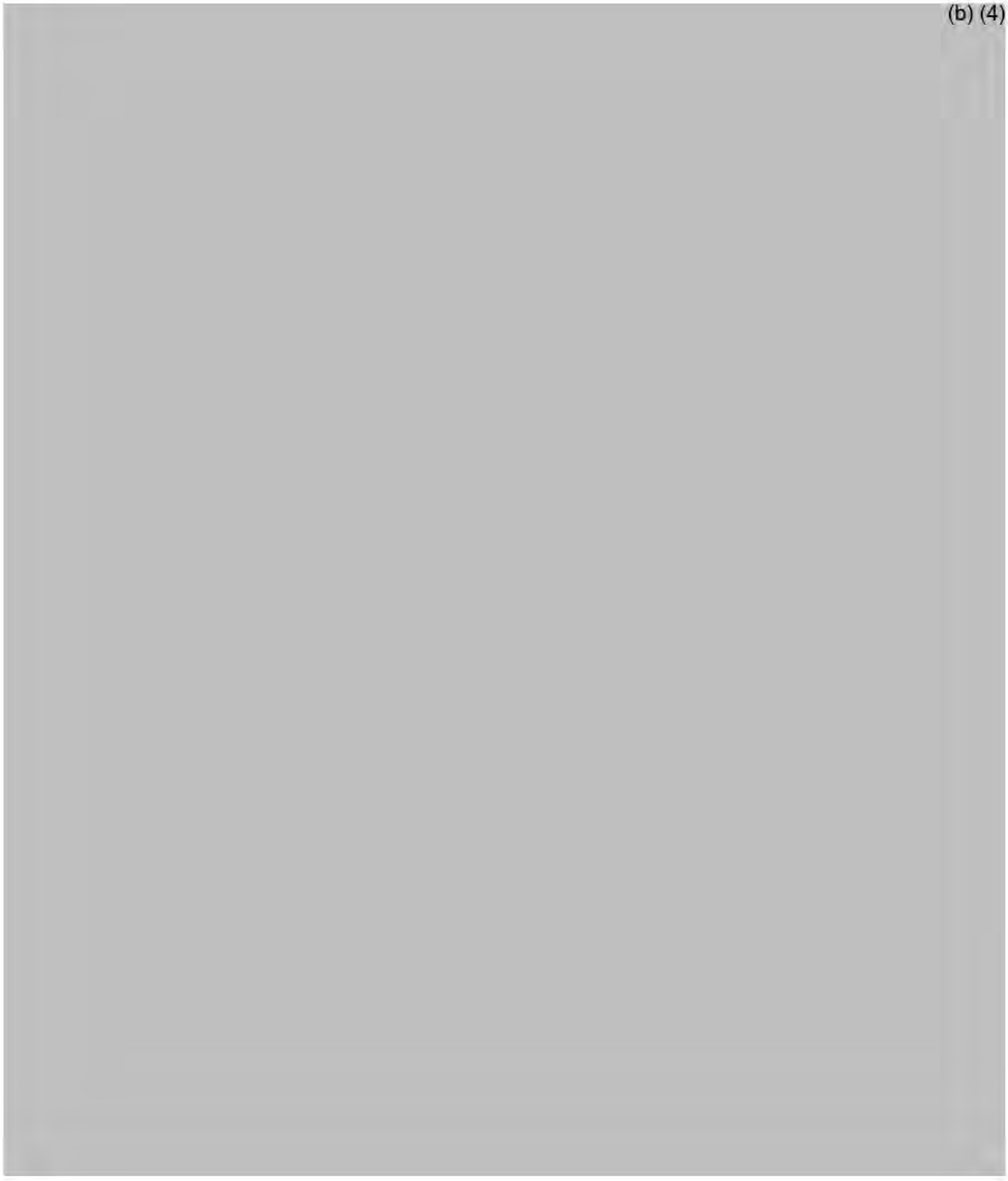

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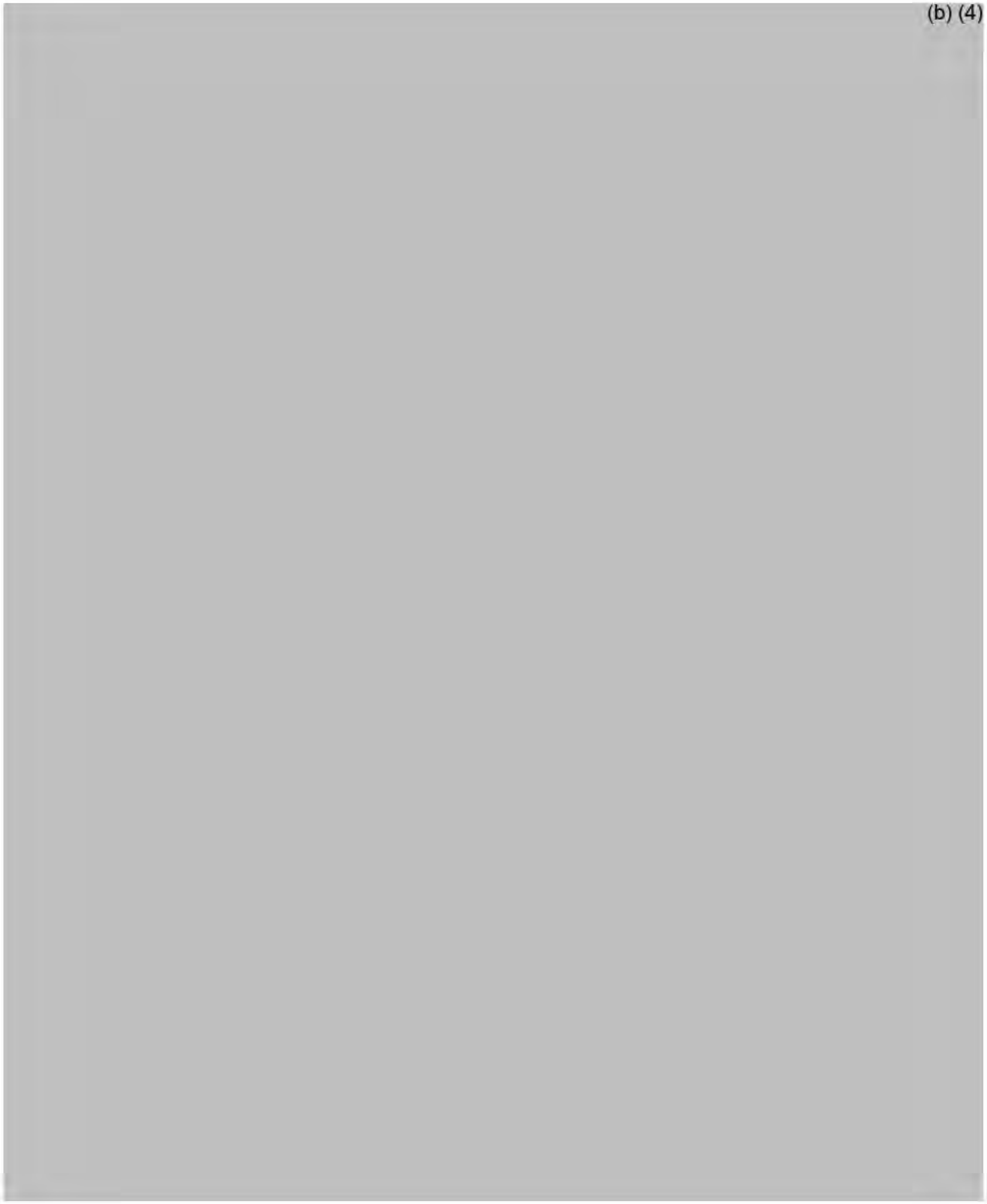

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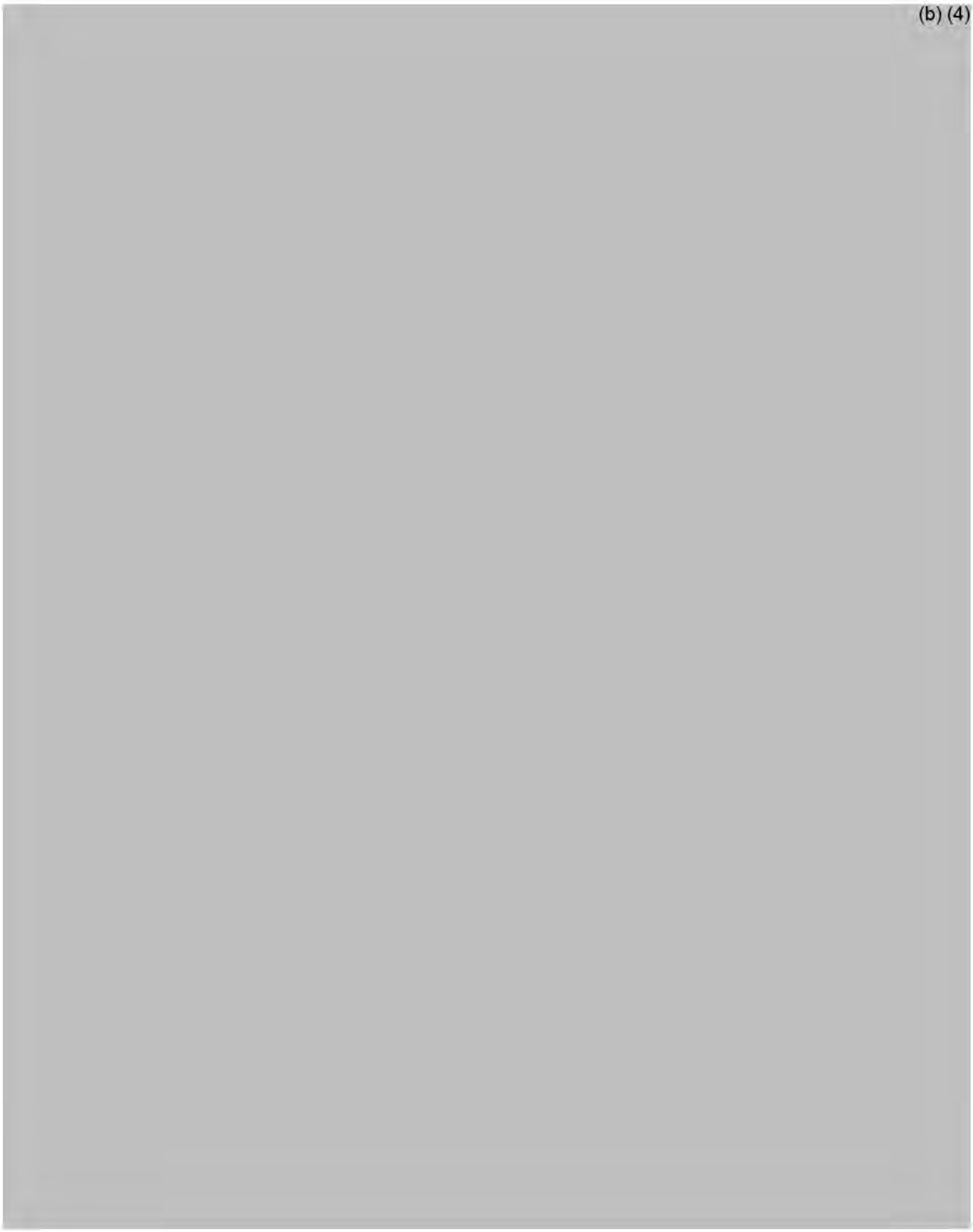

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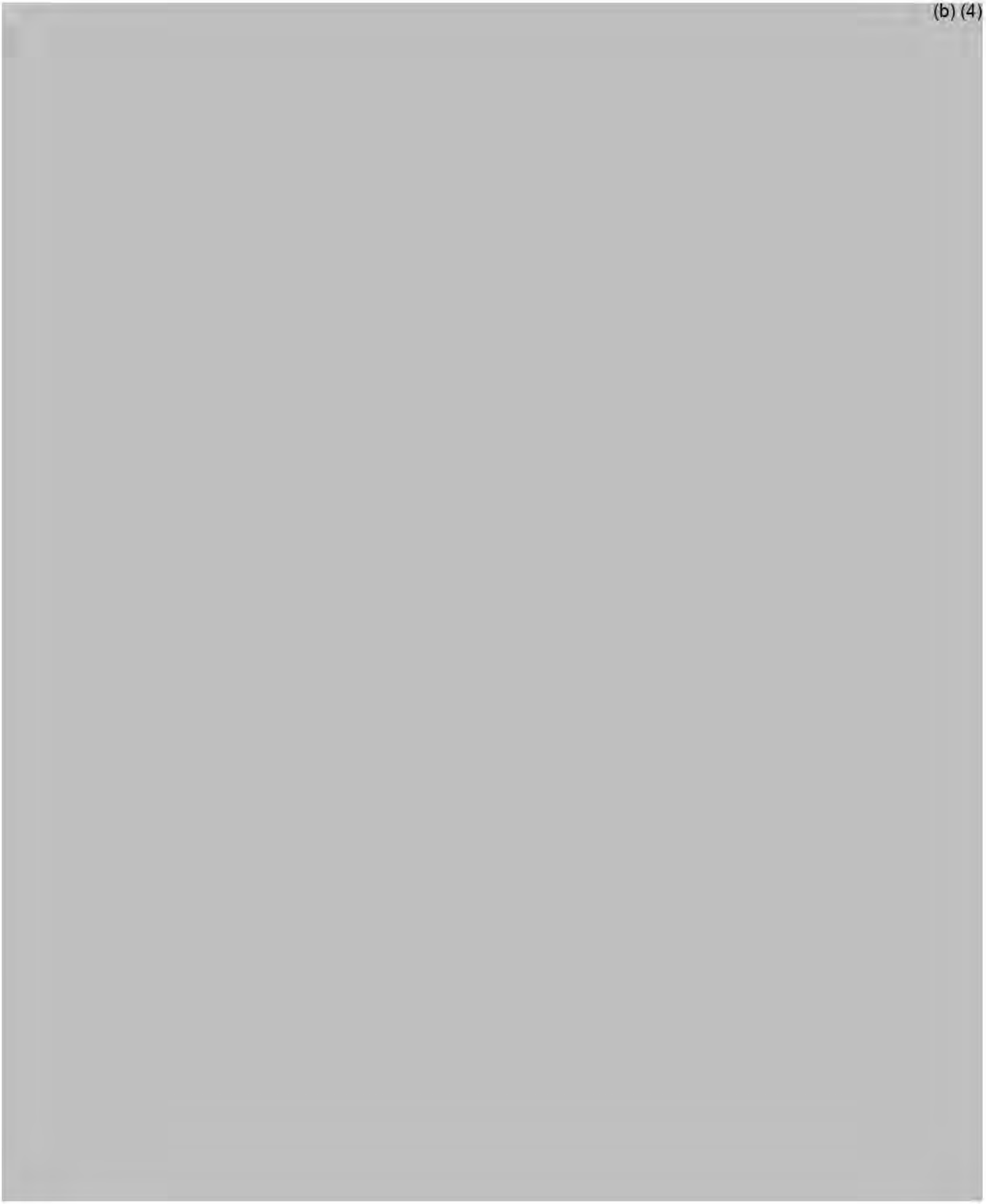

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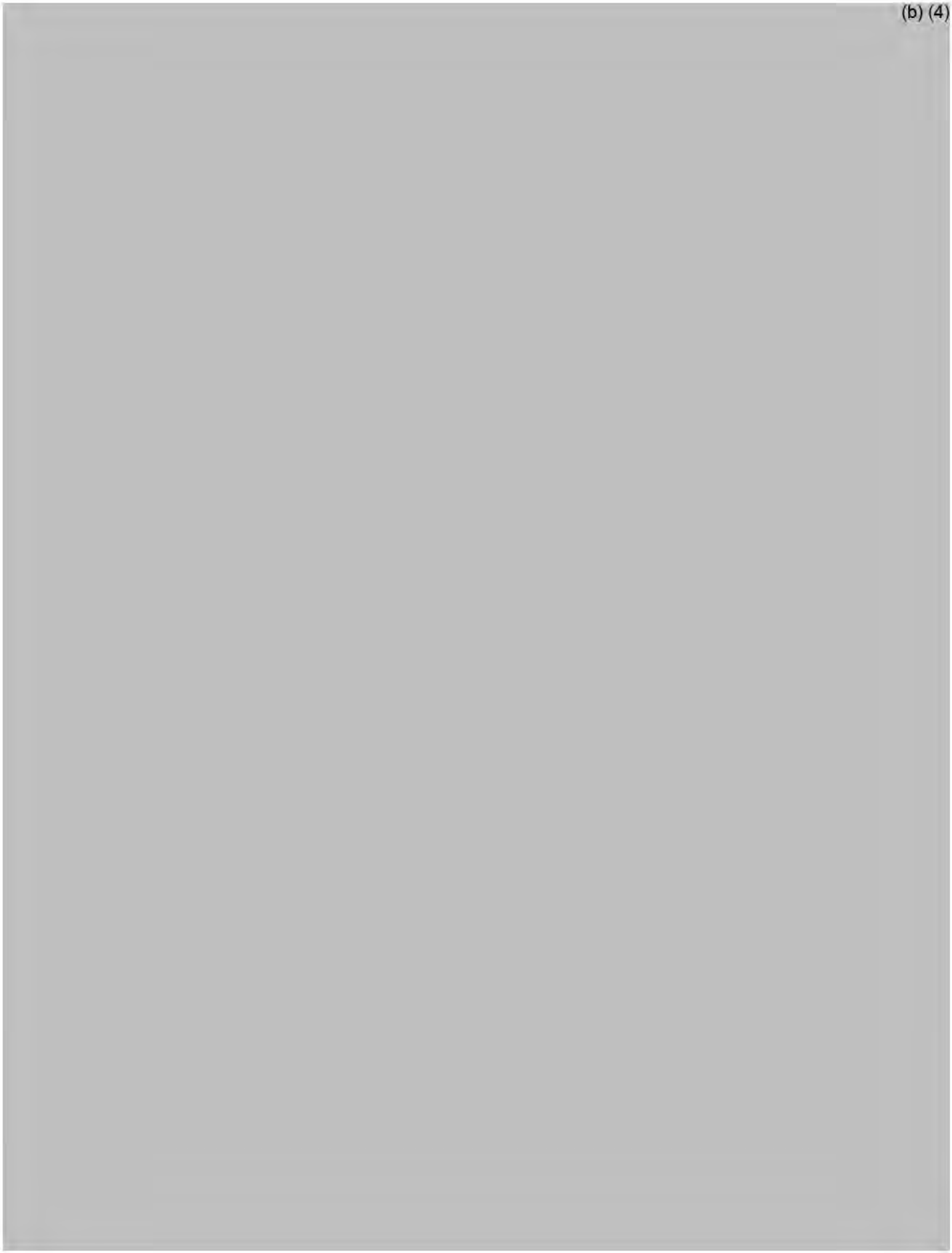

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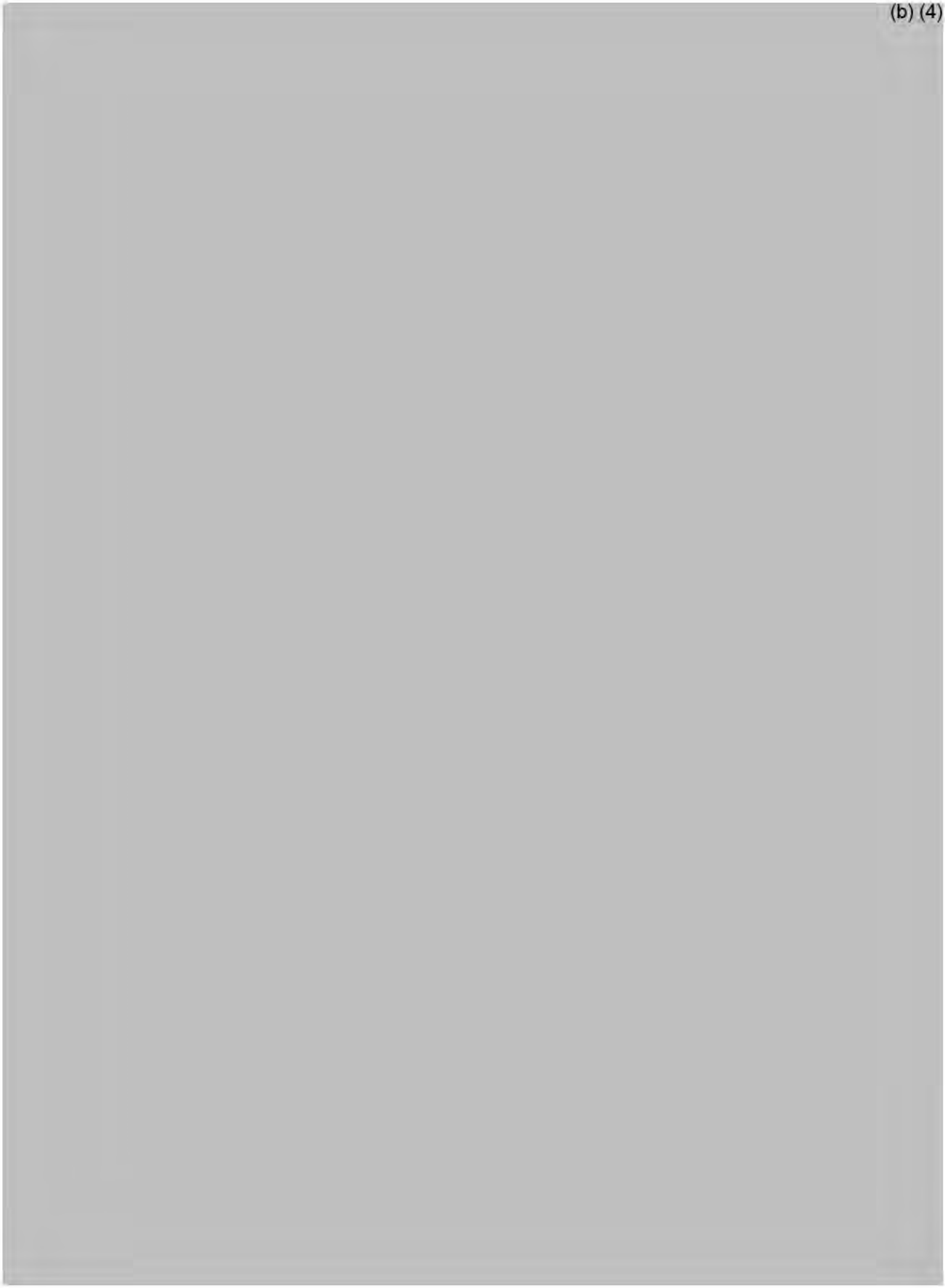

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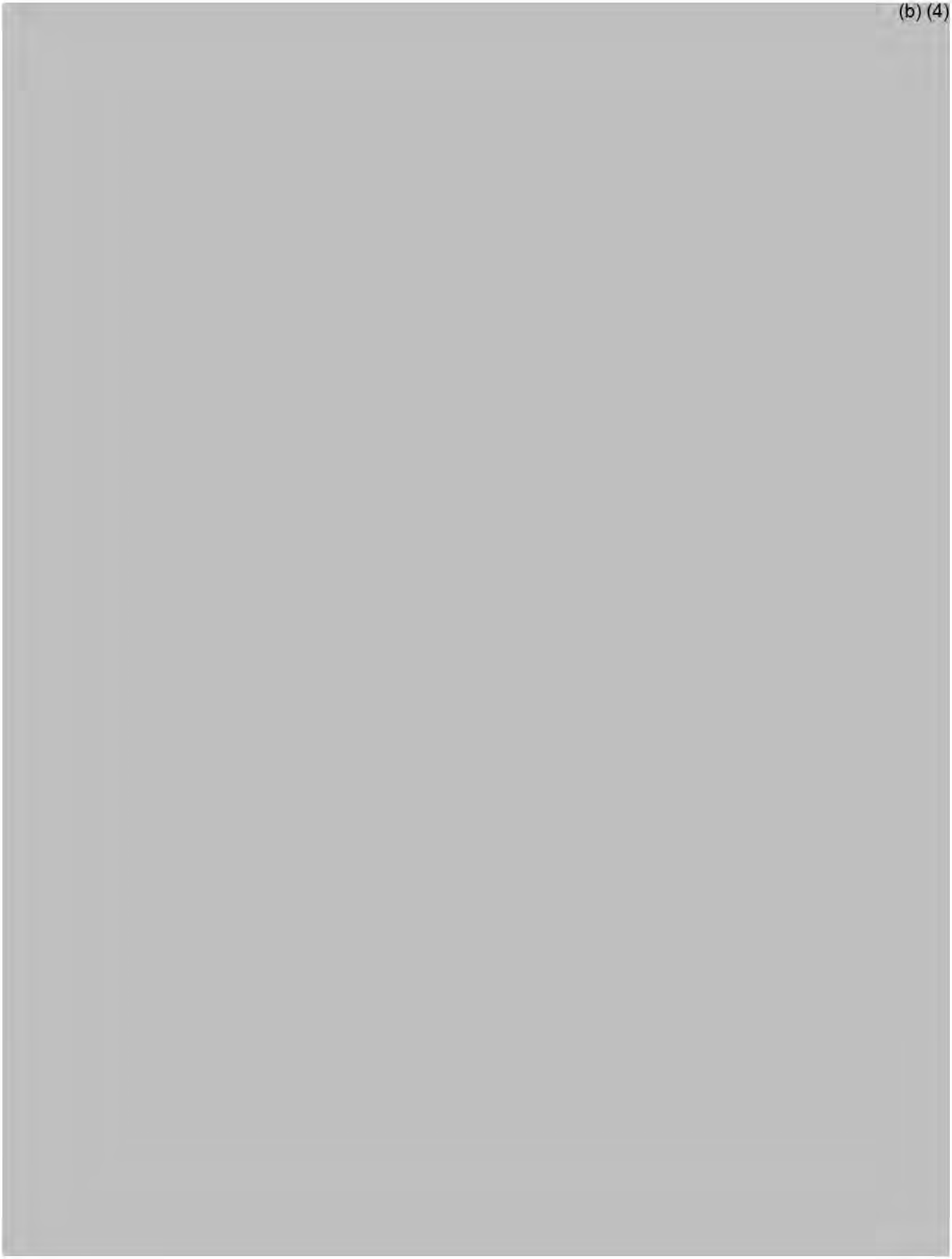

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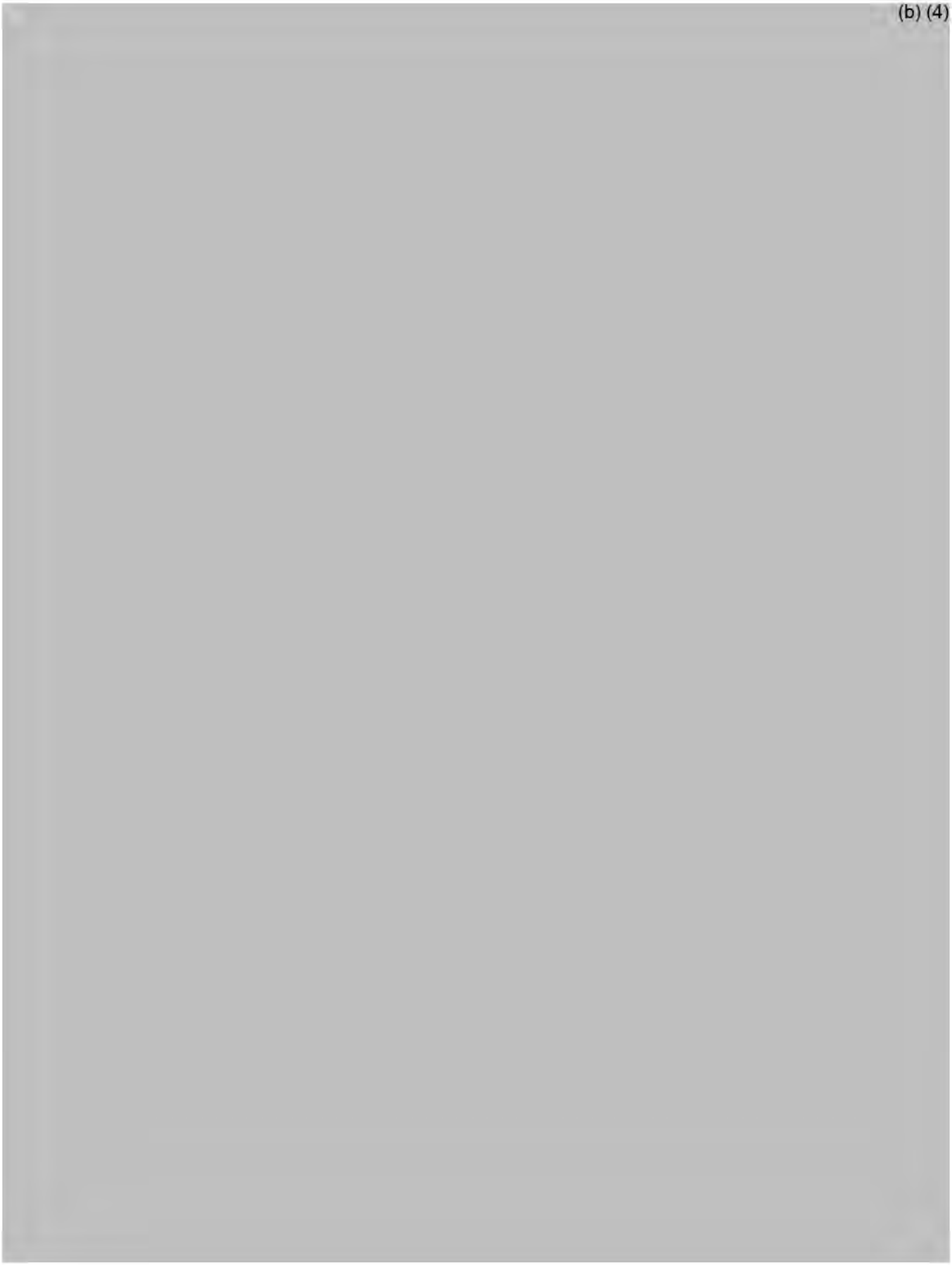

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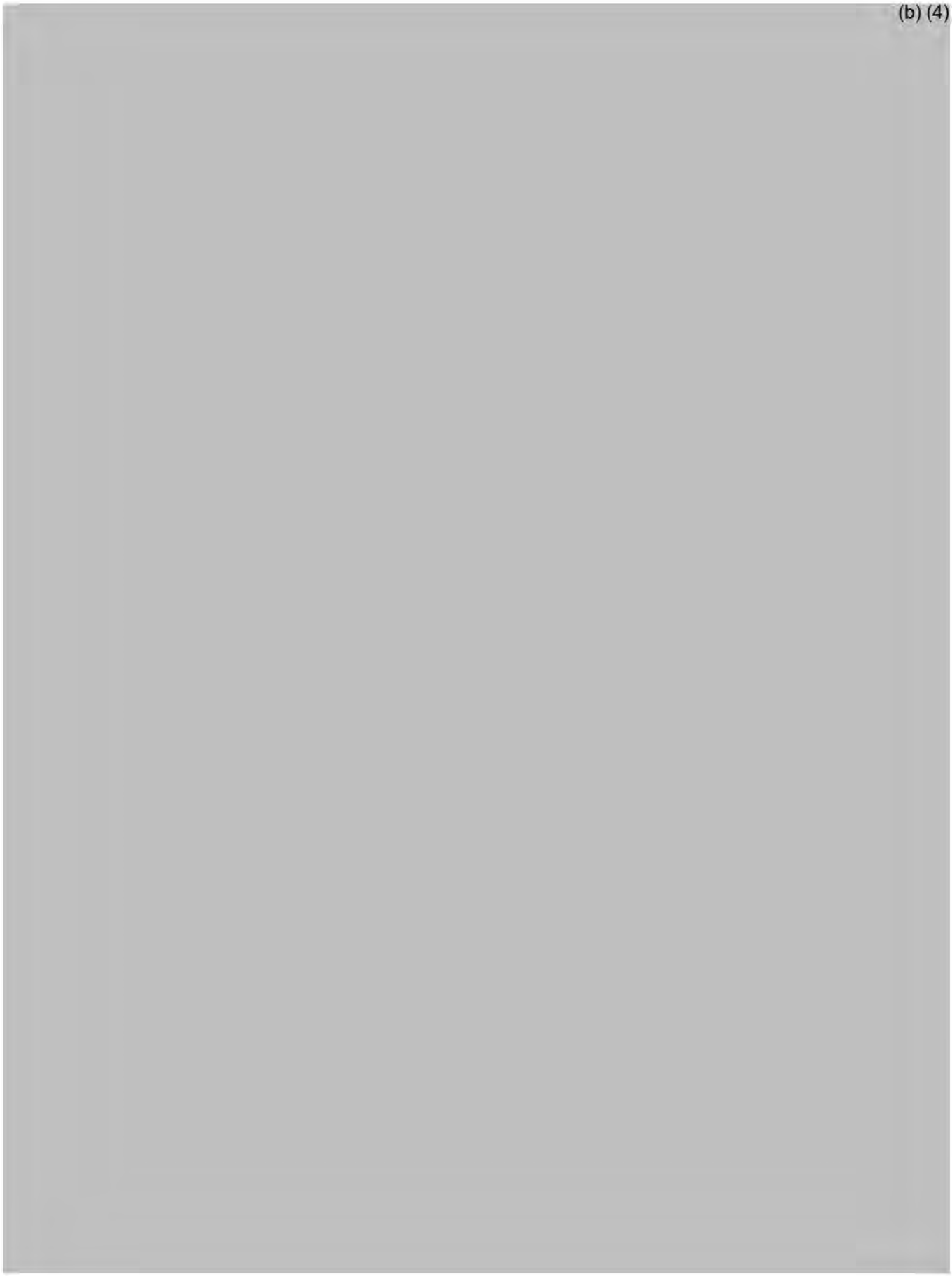


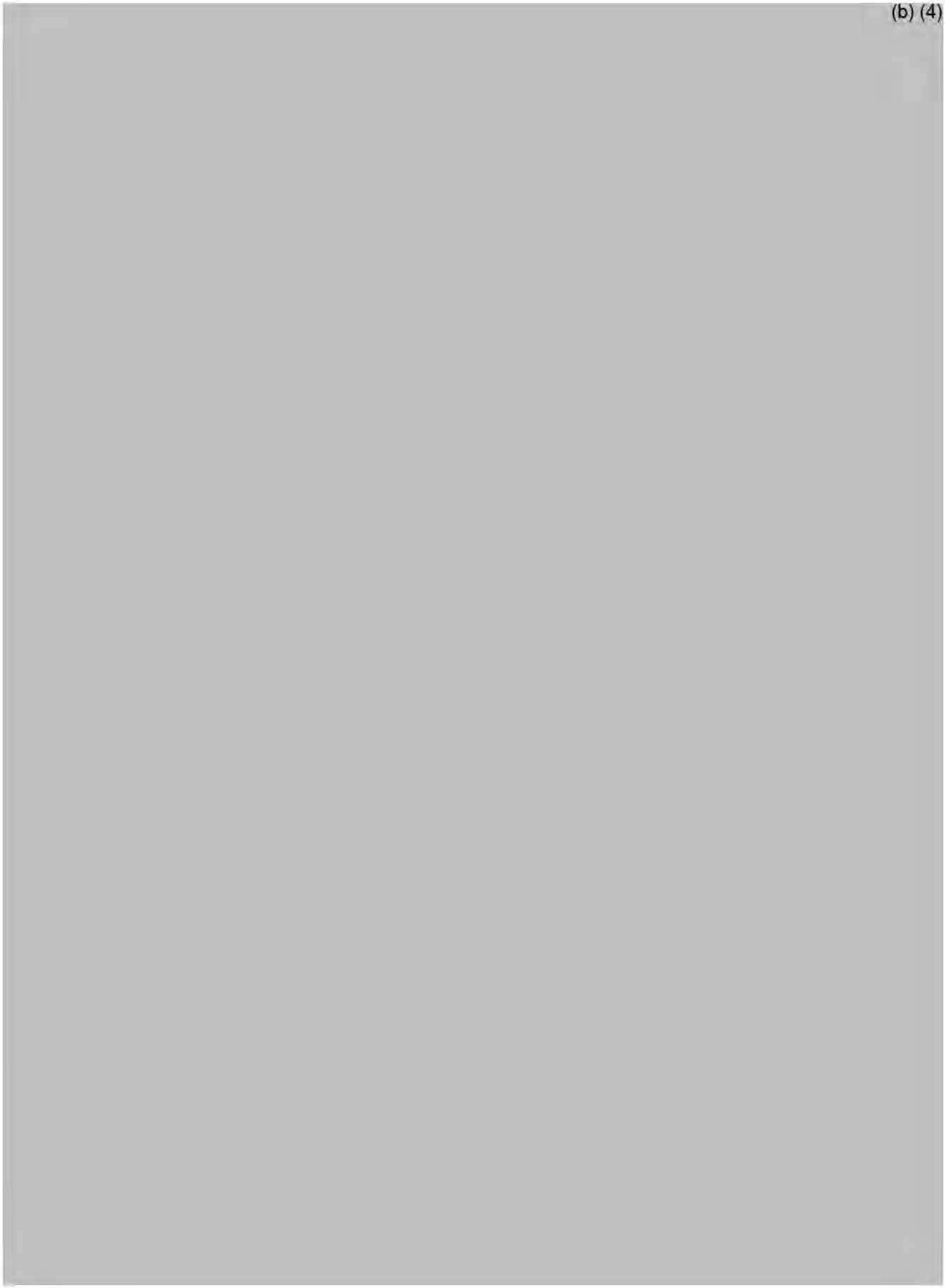


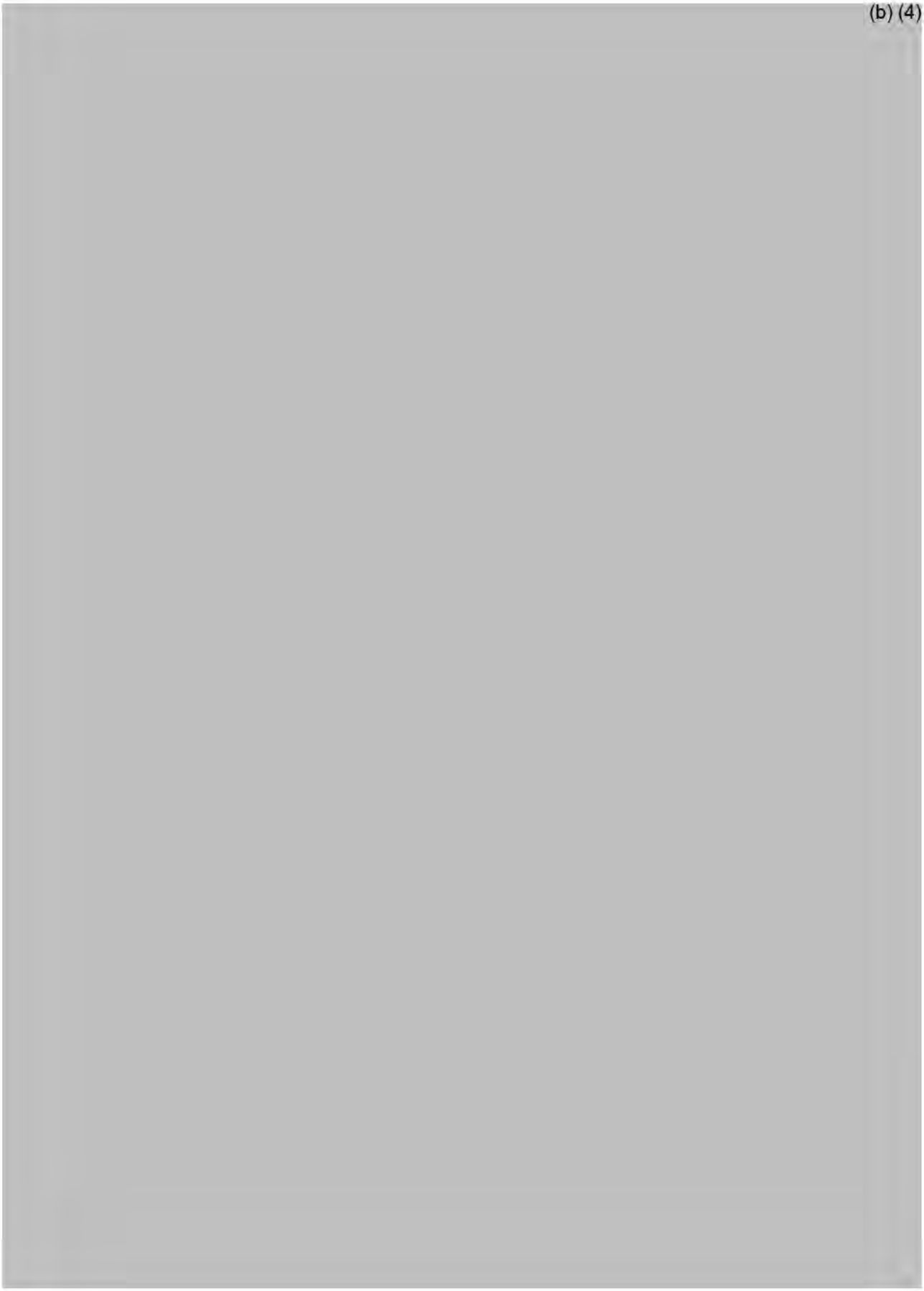

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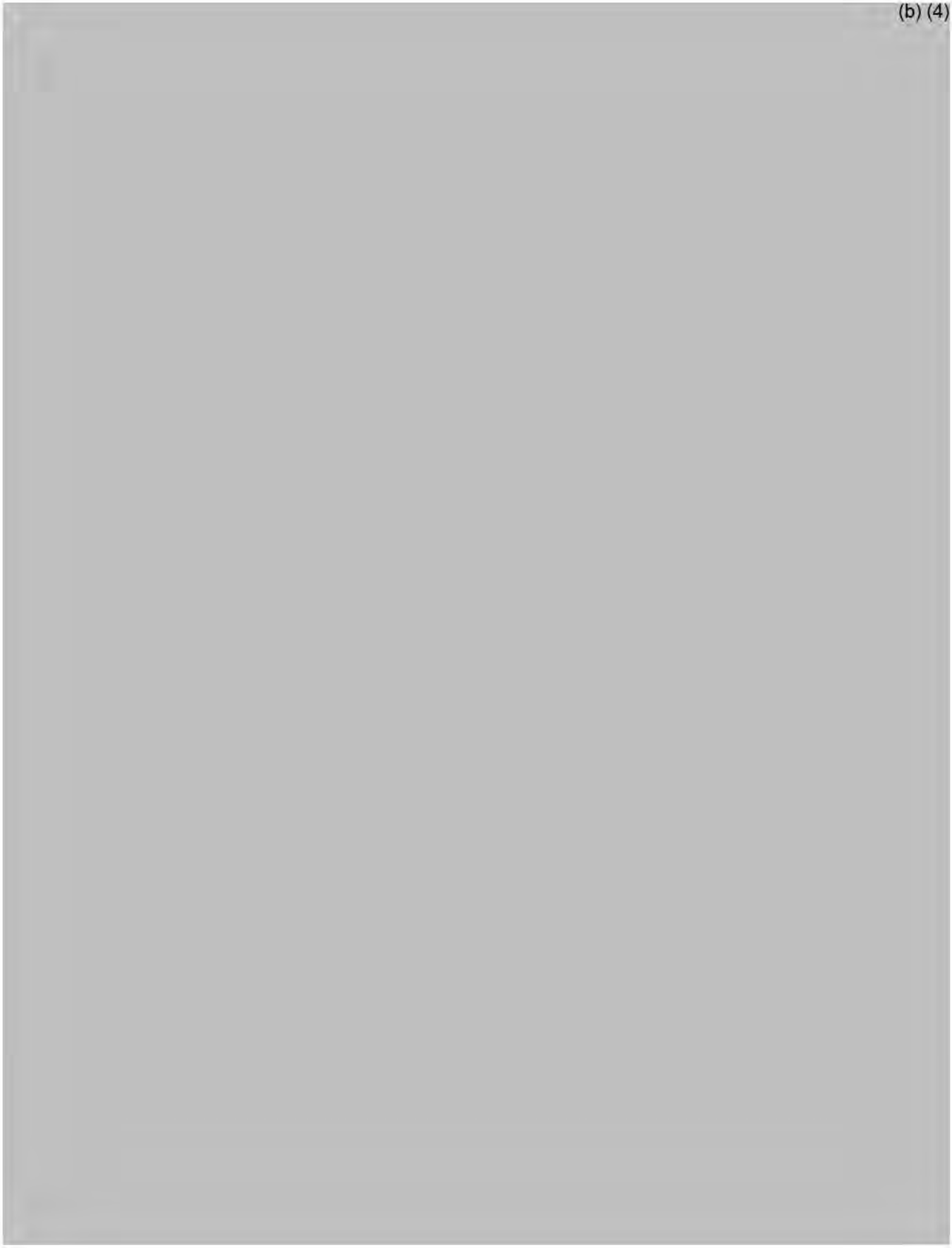


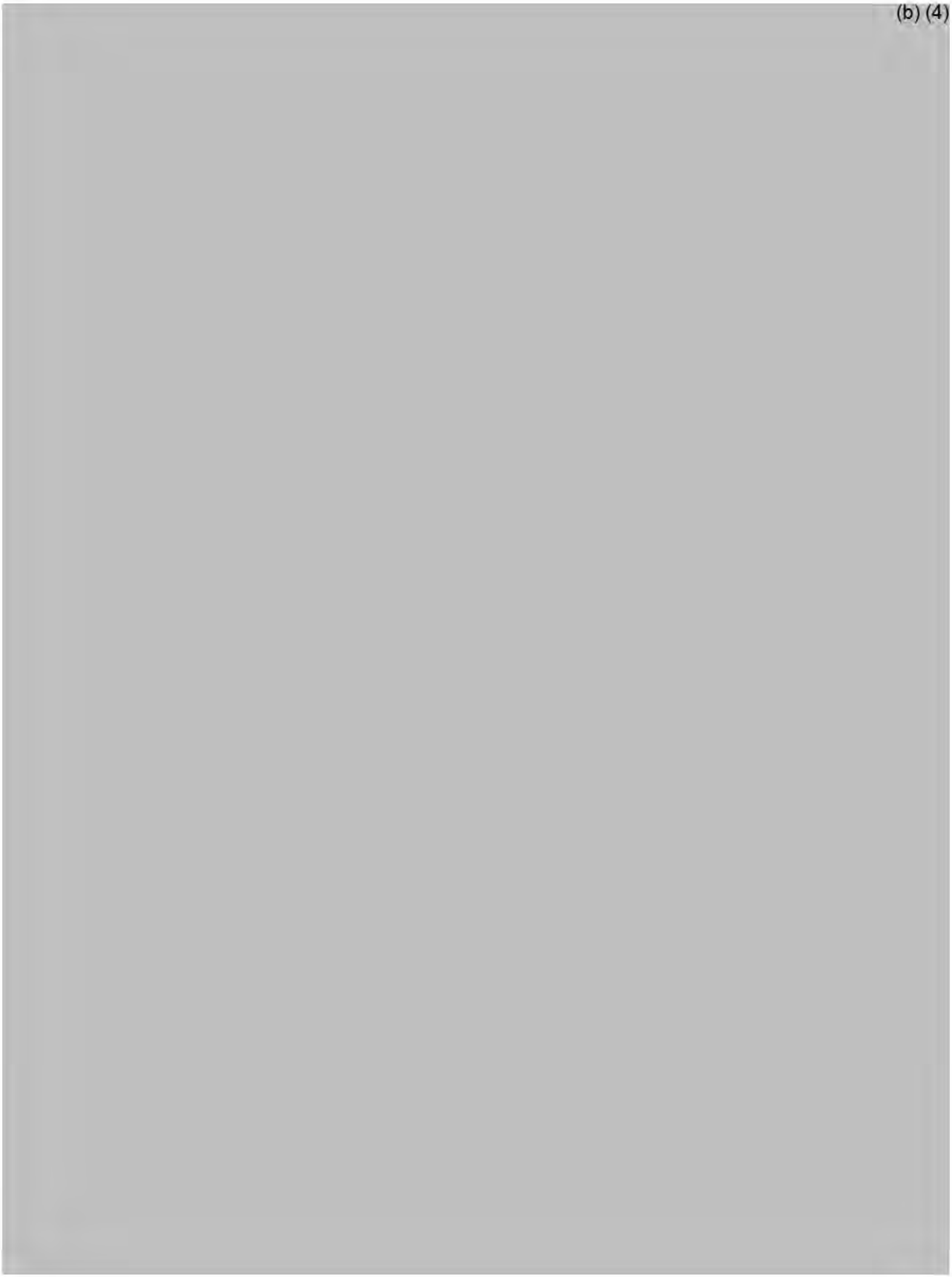


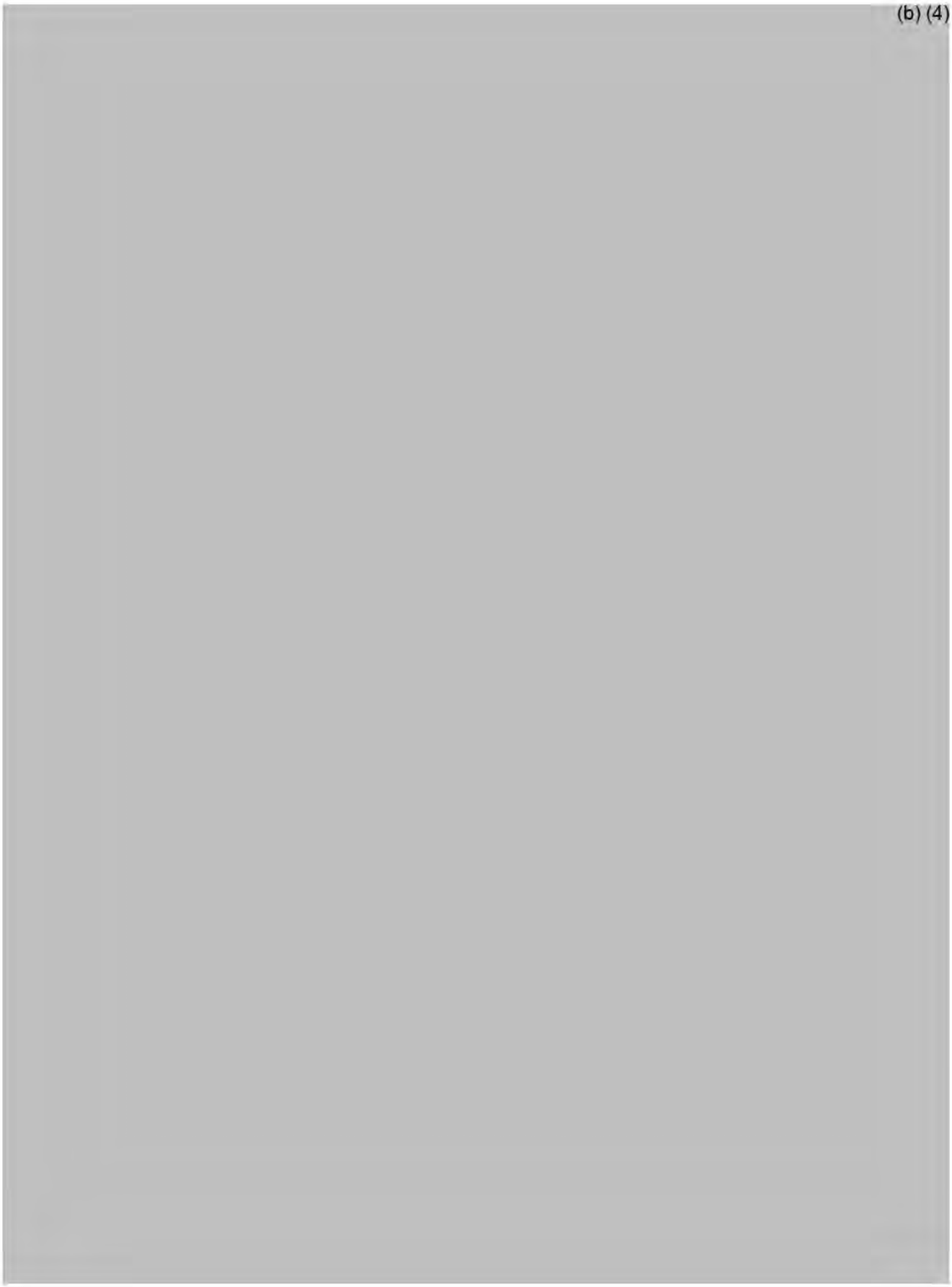







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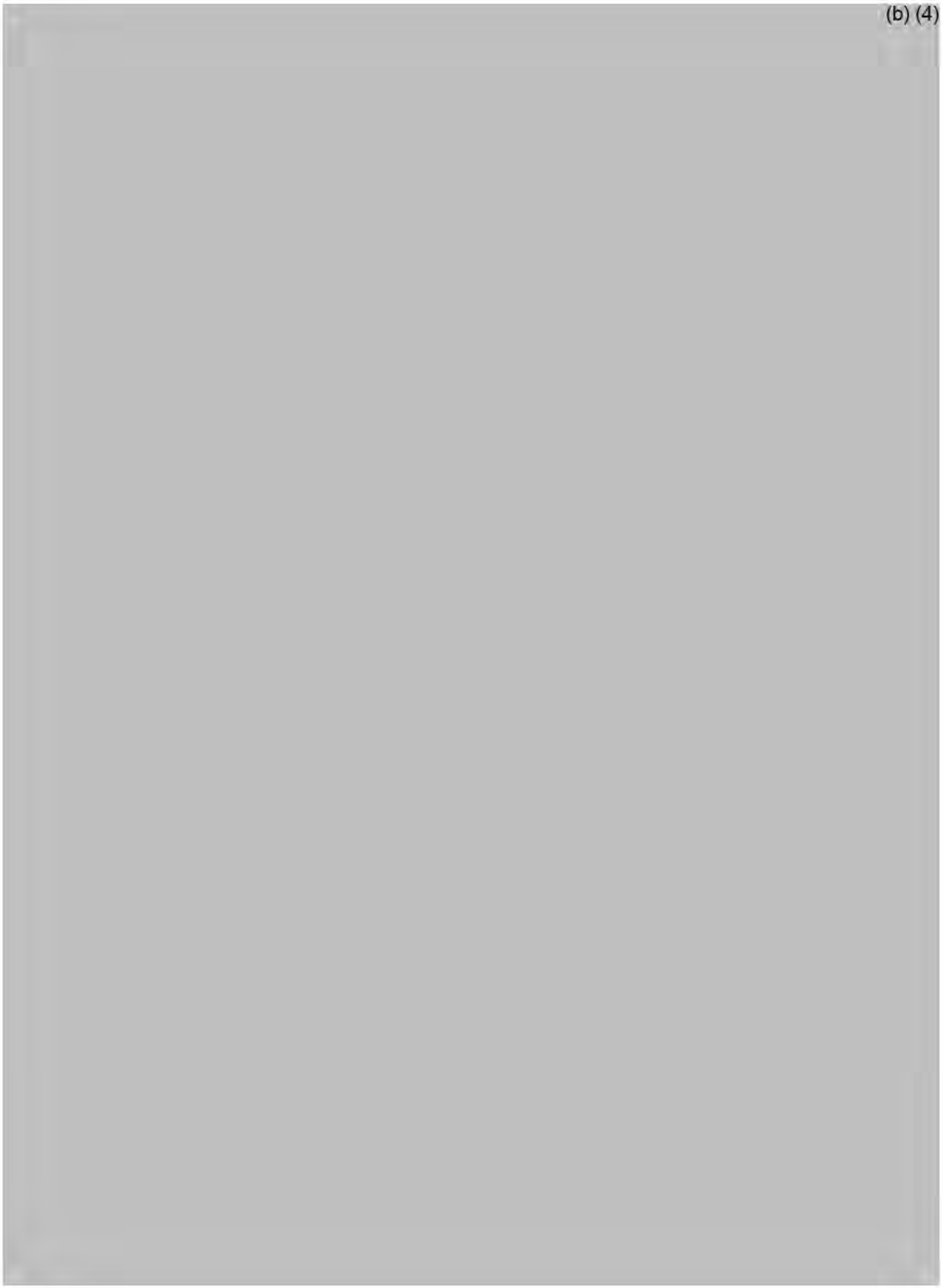
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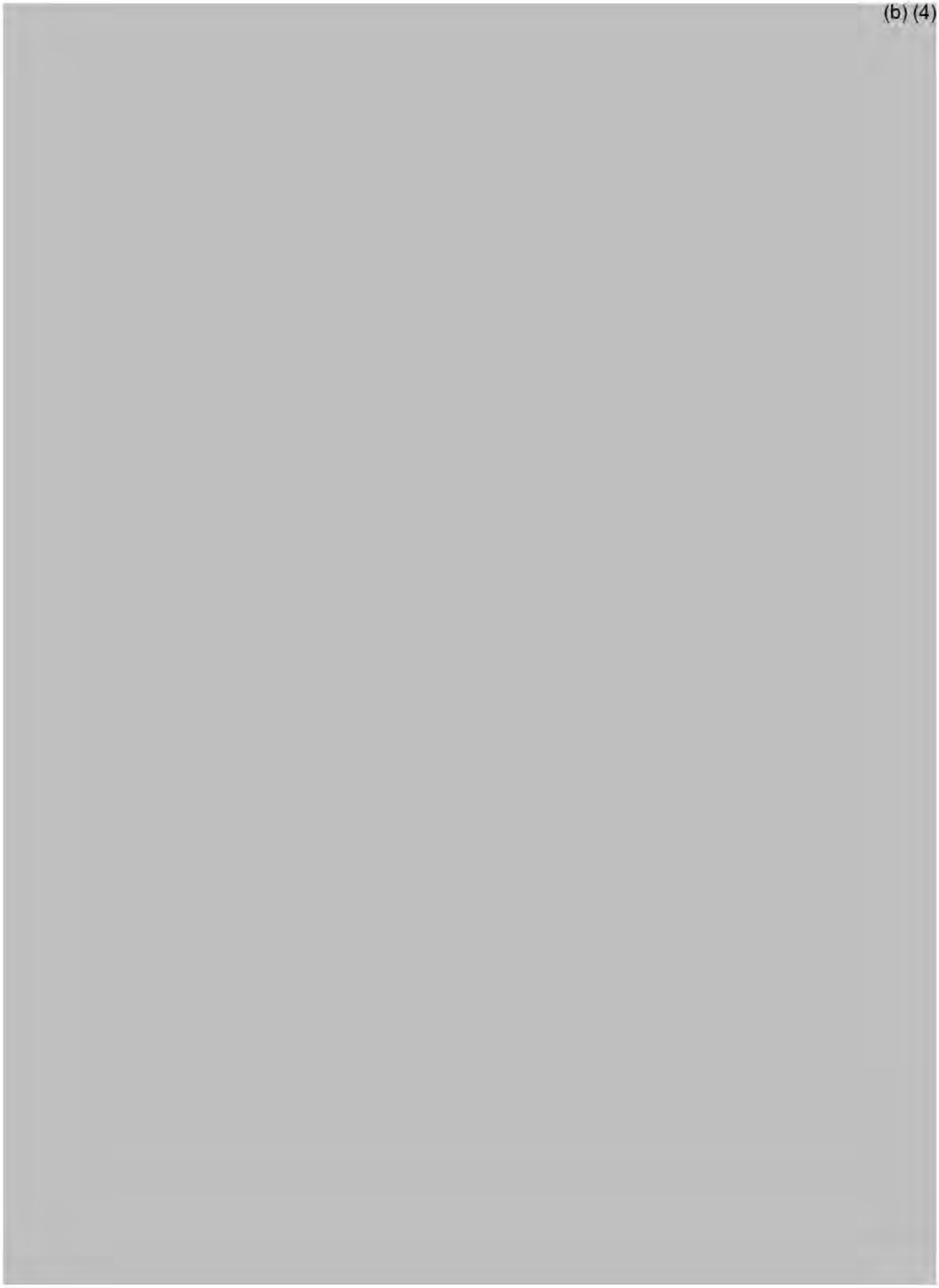
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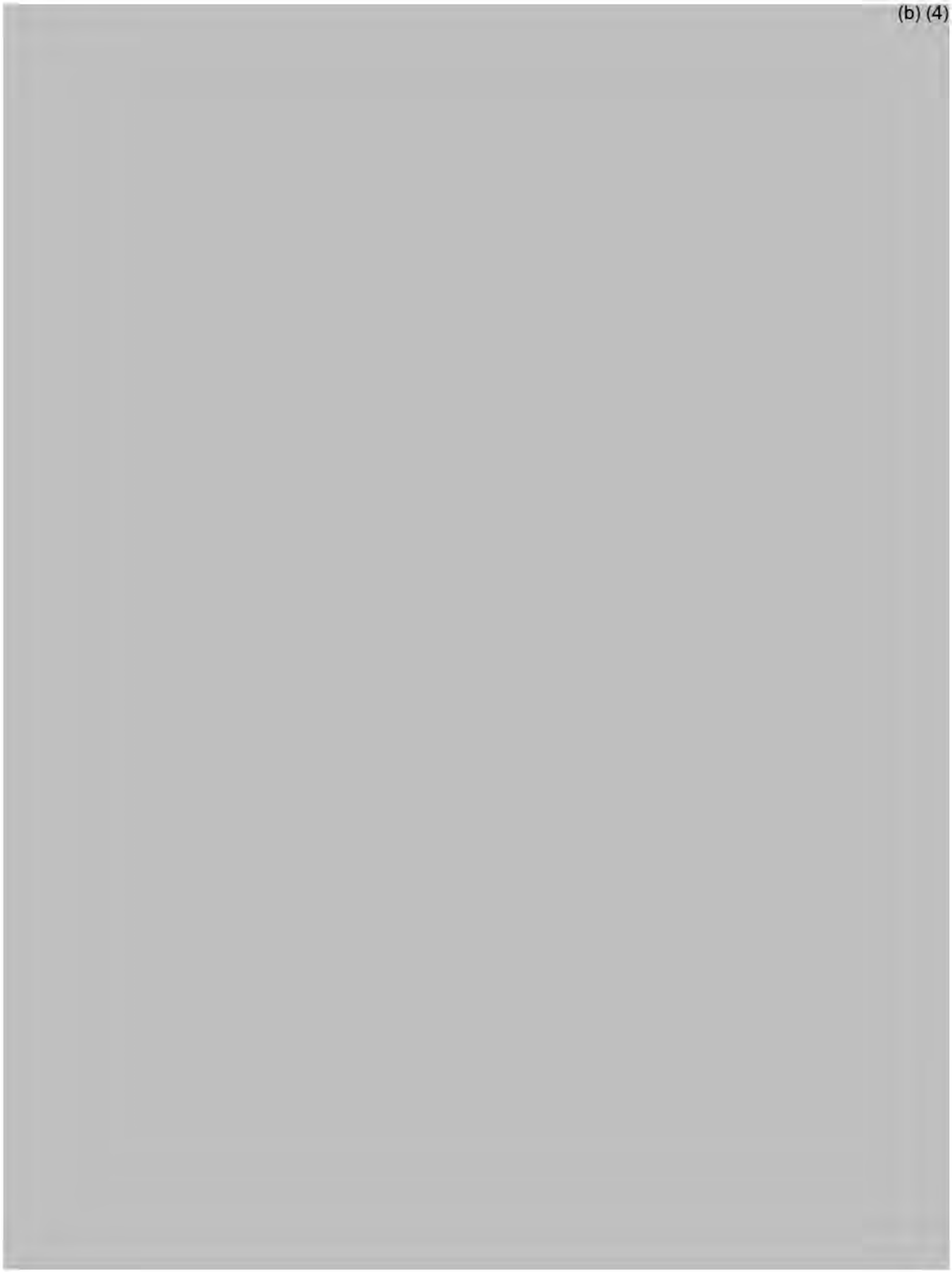
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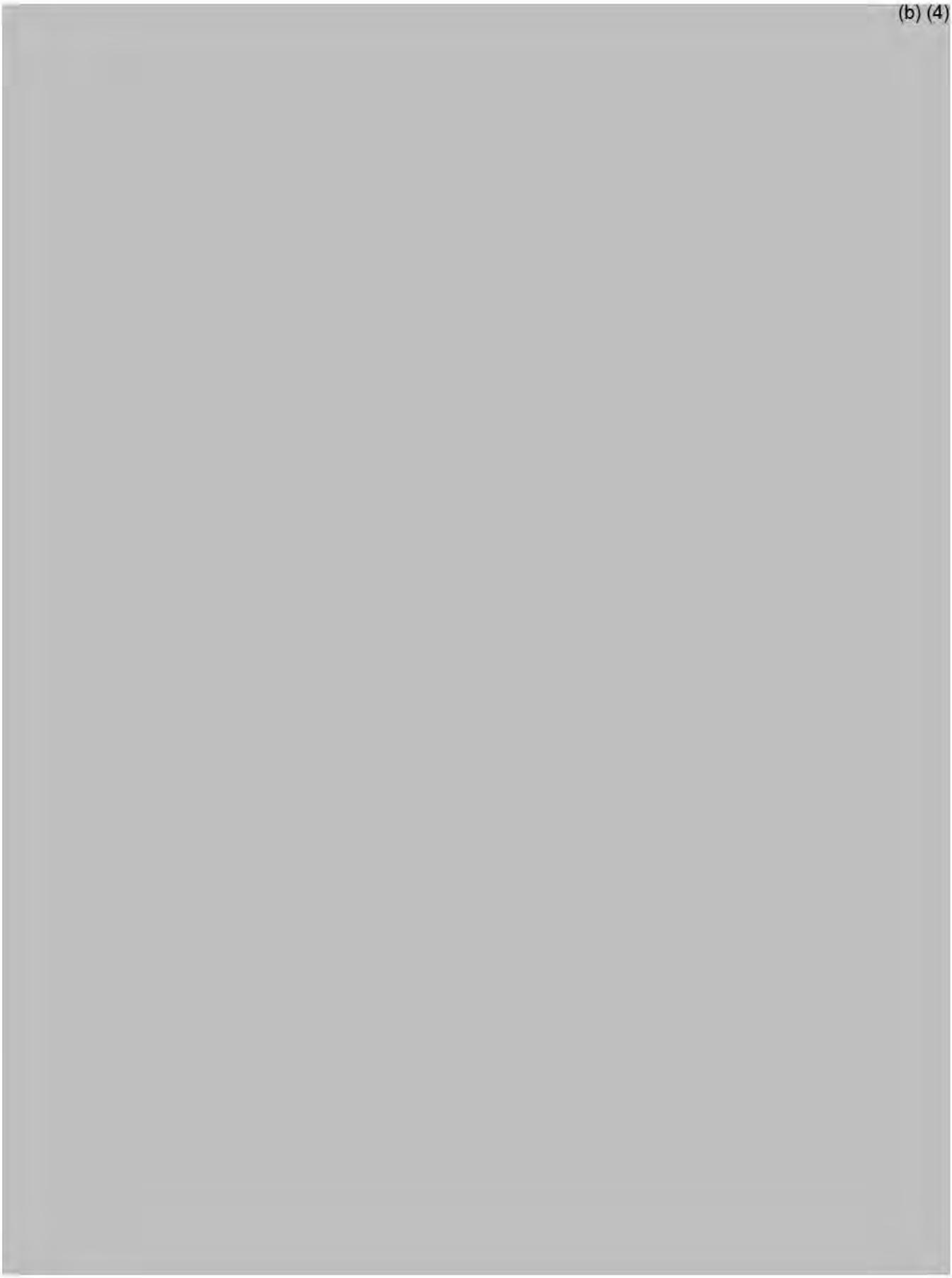
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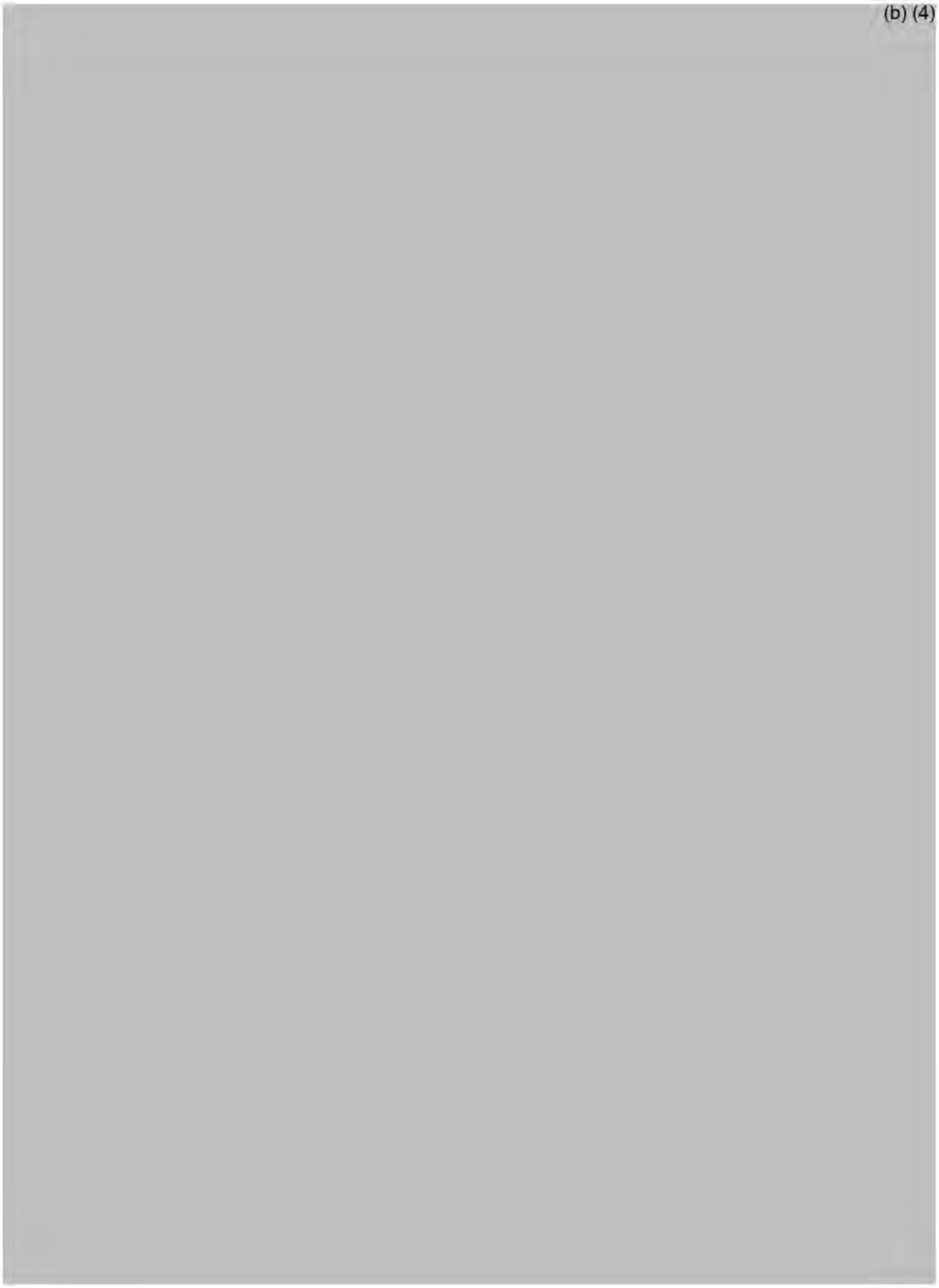


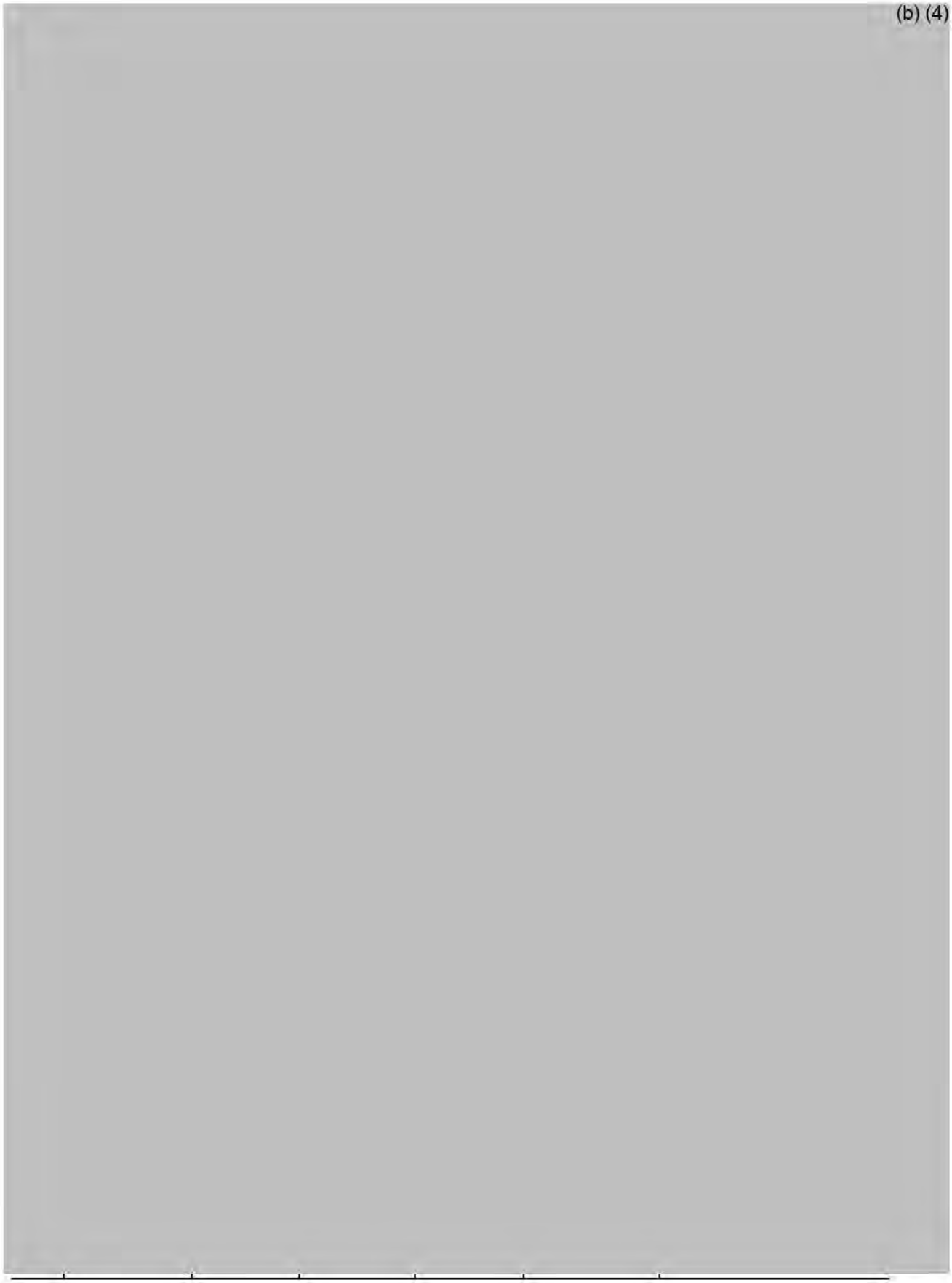



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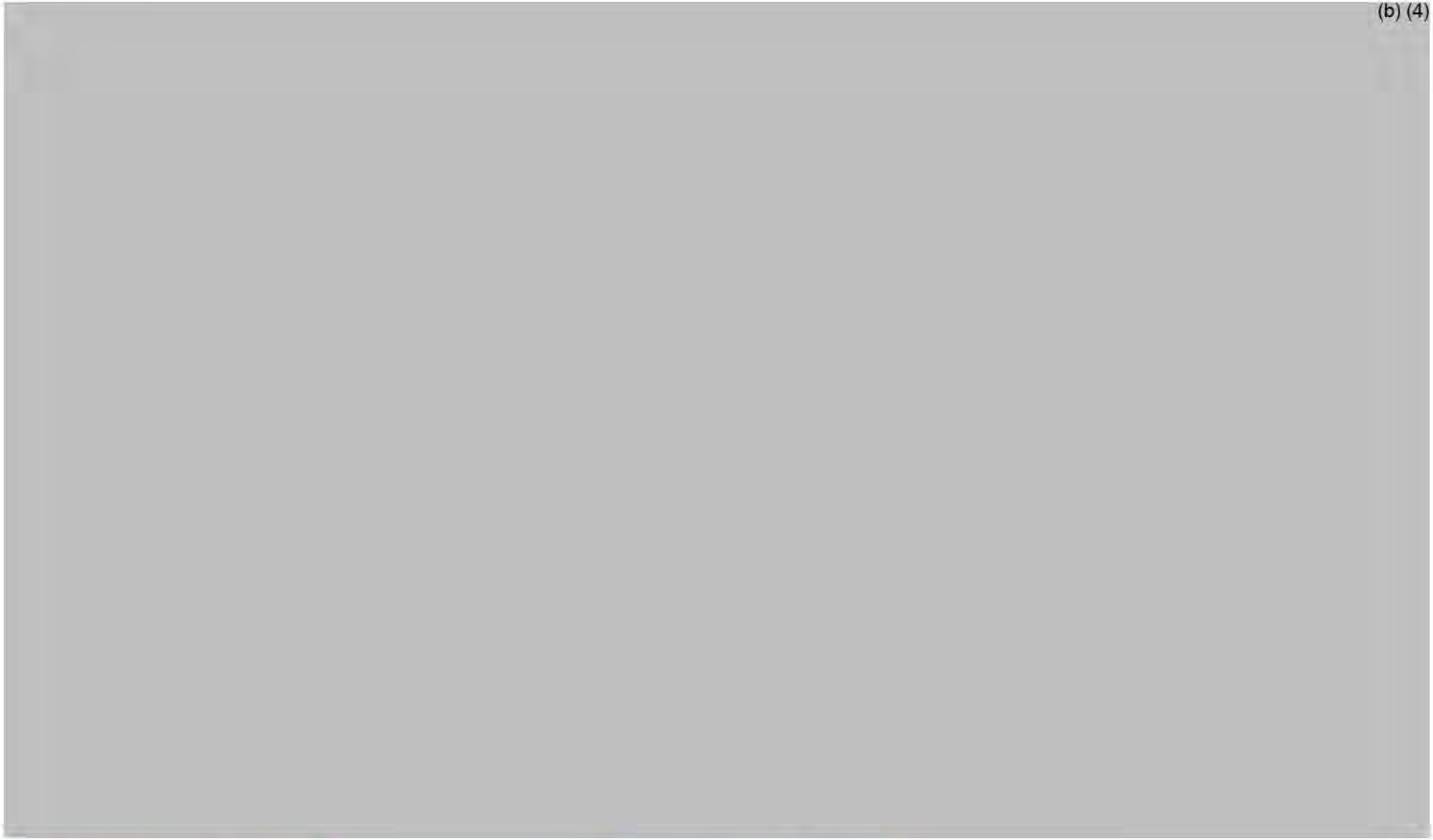



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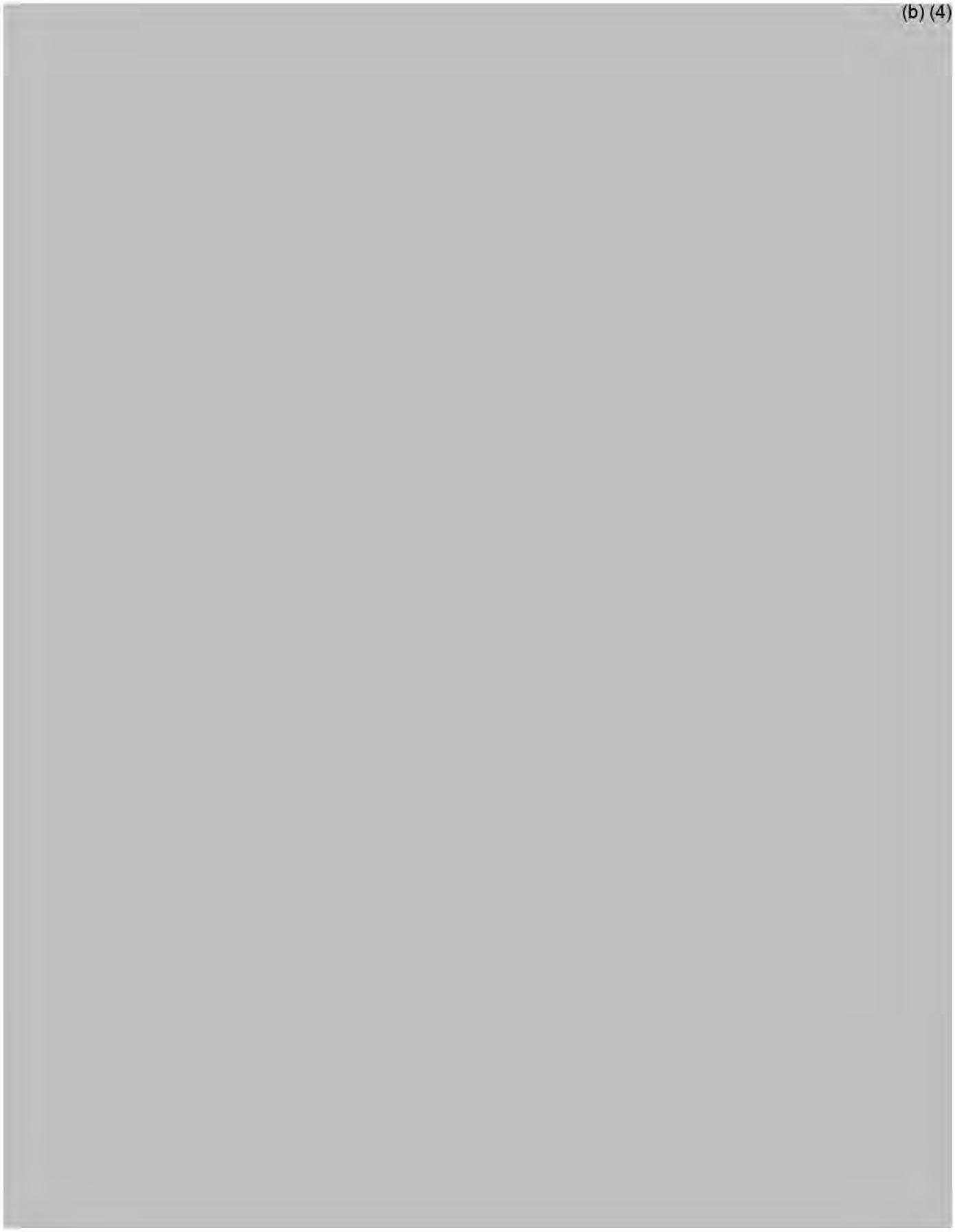

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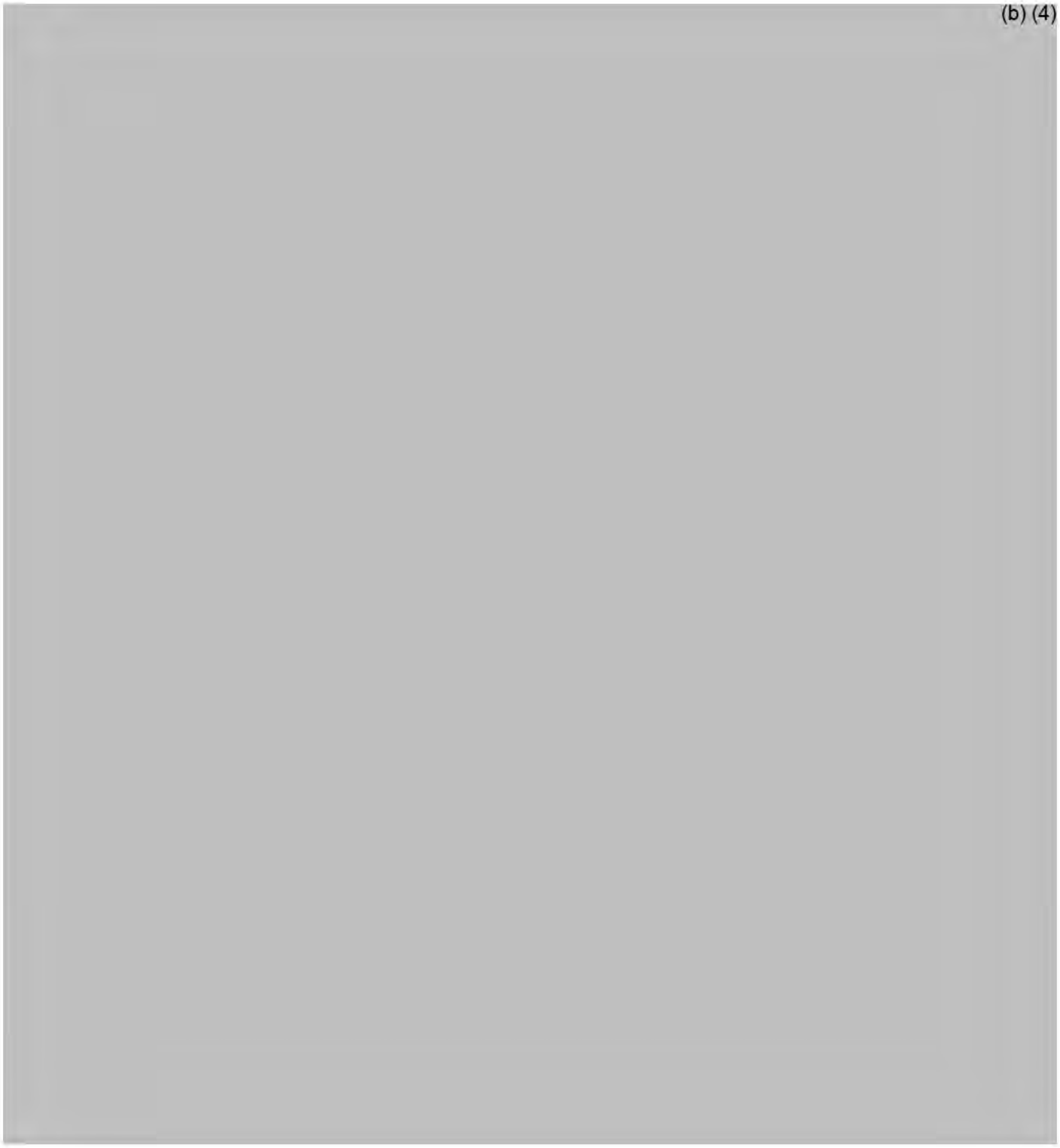

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CONFIDENTIAL REPORT

13C Metabolic flux analysis of *C. glutamicum* KCCM 80346

Version 1.0

TITLE

13C Metabolic flux analysis of *C. glutamicum* KCCM 80346

OBJECTIVE OF THE STUDY

13C Metabolic flux analysis was conducted to determine intracellular fluxes of *C. glutamicum* KCCM 80346.

SCHEDULE OF THE STUDY

Initiation of experiment: August 16 2021

Termination of experiment: October 8, 2021

Submission of final report: October 15, 20201

TESTING FACILITY

R&BD)OMICS Team, CJ CheilJedang
55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do 16495, Korea

RESPONSIBLE STAFFS

Analyst and Author	(b)(6)
Report approved by	

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INTRODUCTION

Microbes naturally synthesize various chemicals through enzymatic reactions. However, as their metabolism is evolved for surviving under natural environment, the yields of high-value chemicals are generally too low to meet industrial demand.

Metabolic engineering such as knockout of genes related to by-product synthesis, overexpression of related genes to product synthesis or introduction of heterologous genes might re-direct cellular metabolism from that of optimized for growth to optimize for high-value chemical production (Lee et al., 2009; Liu and Nielsen, 2019).

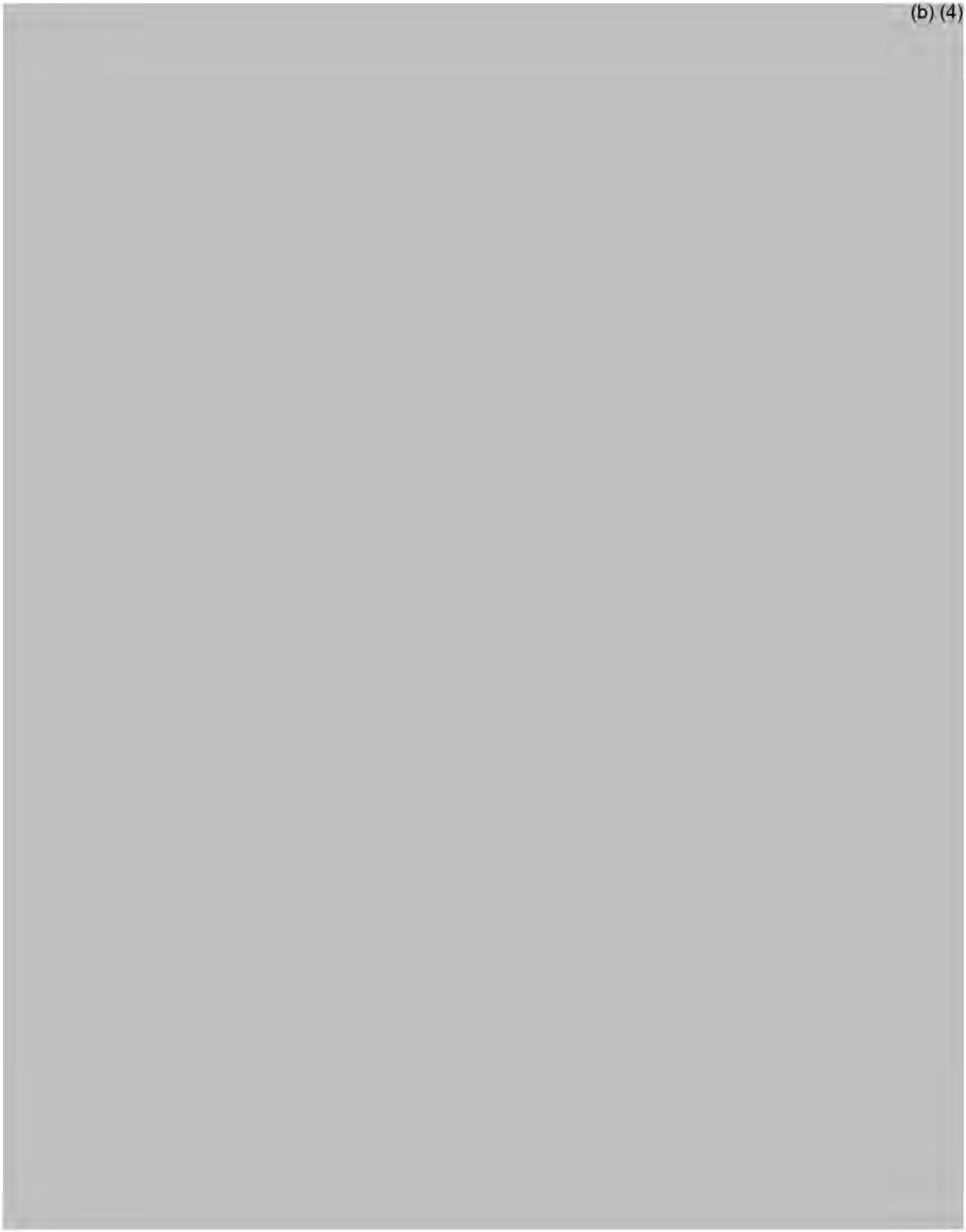
Metabolic flux could provide priceless information for understanding cellular metabolism since it is the final output of multi-level based metabolic regulations such as transcription and translation (Sauer, 2004). 13C metabolic flux analysis (13C MFA) is one of the most powerful approaches for quantifying metabolic fluxes with combination of extracellular flux measurements and isotope labeling patterns of intracellular metabolite and has been extensively used to determine intracellular fluxes of many organisms (Chen et al., 2011; Liu and Stephanopoulos, 2016; Ahn et al., 2016) .

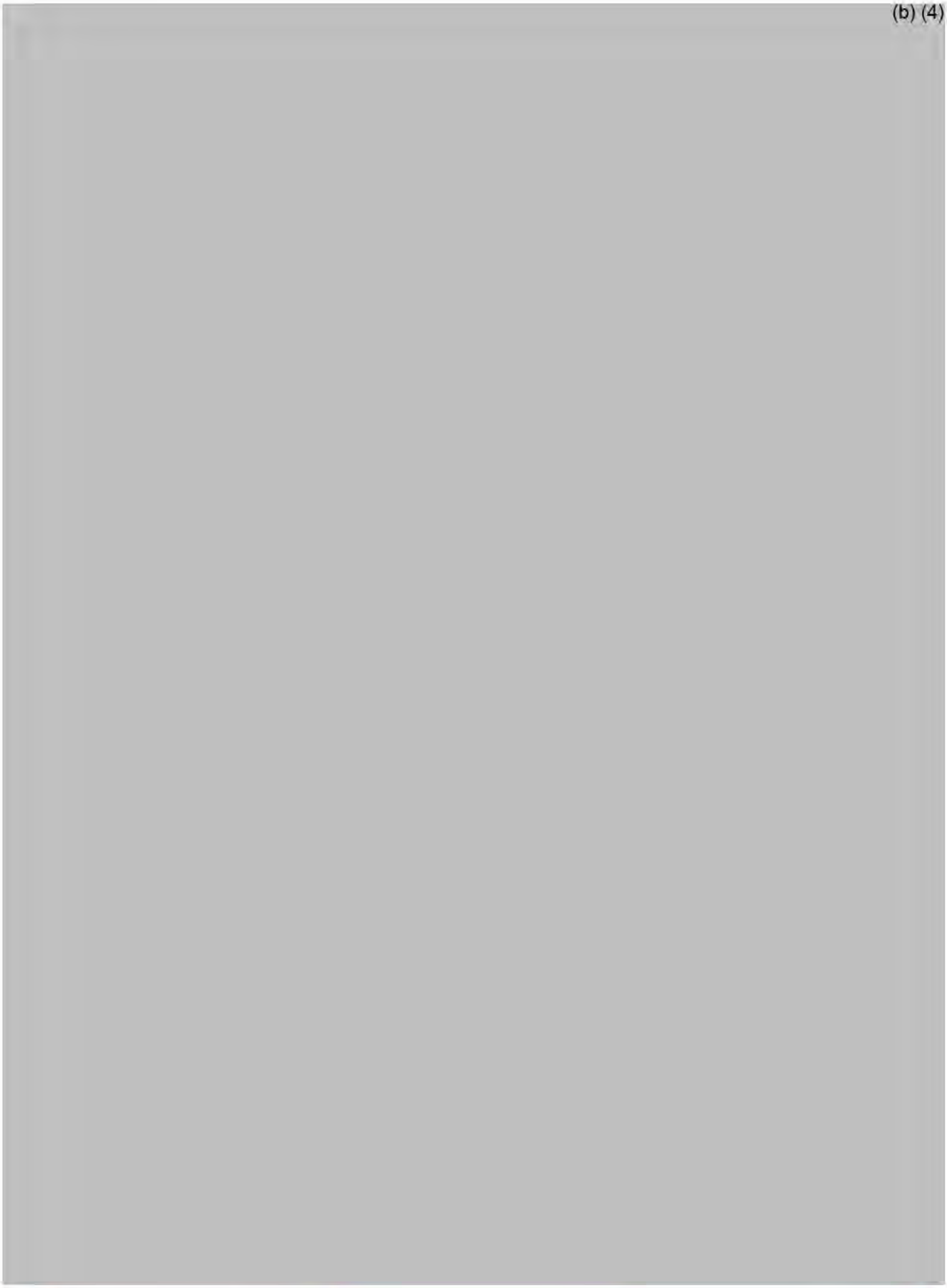
Here, we report re-directed metabolic fluxes of production strain, *C. glutamicum* KCCM 80346, compared to those of the wild-type strain, *C. glutamicum* ATCC 13869, through 13C MFA.

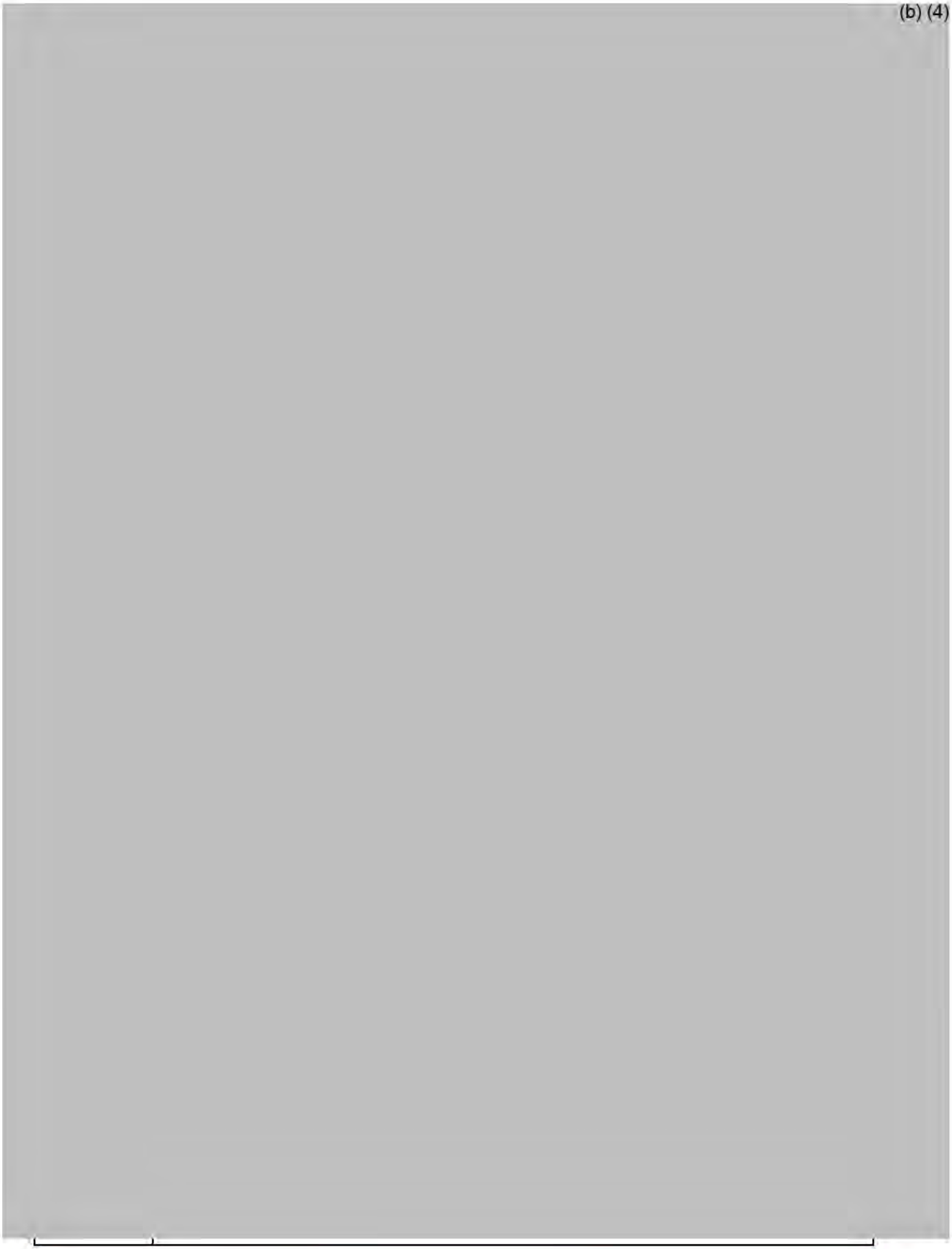
METHODS

Bacterial cultivation with (b)(4) glucose

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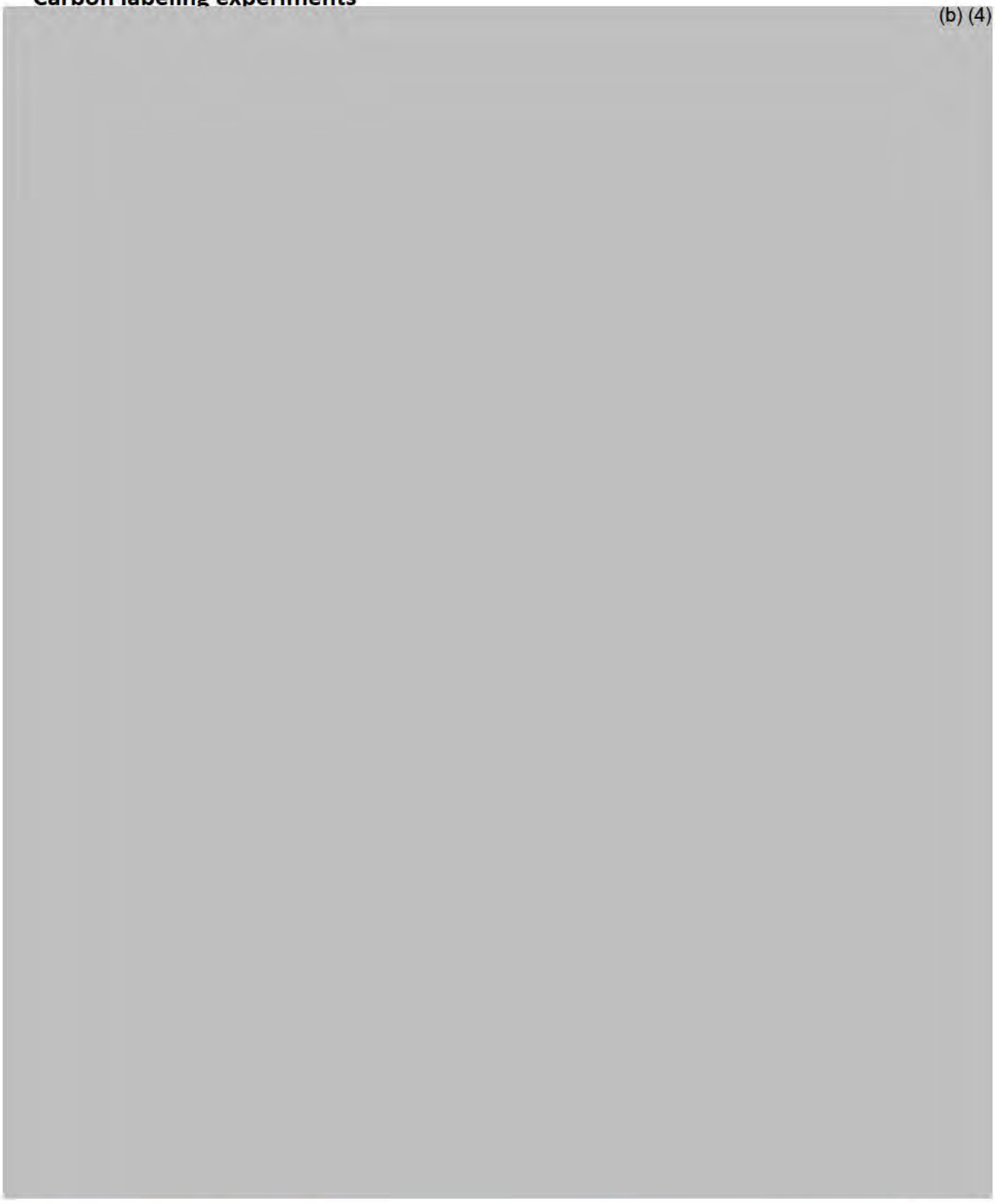


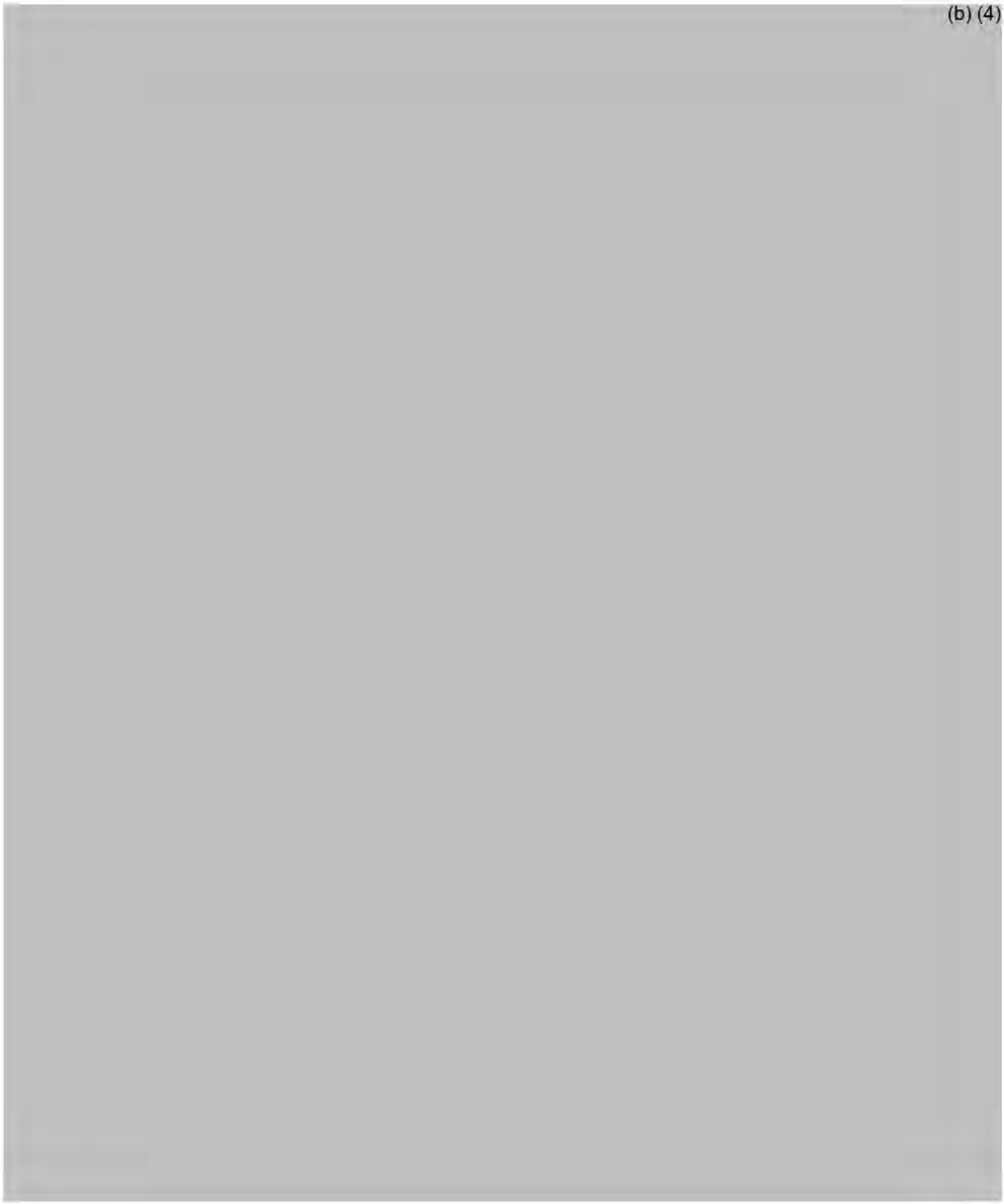

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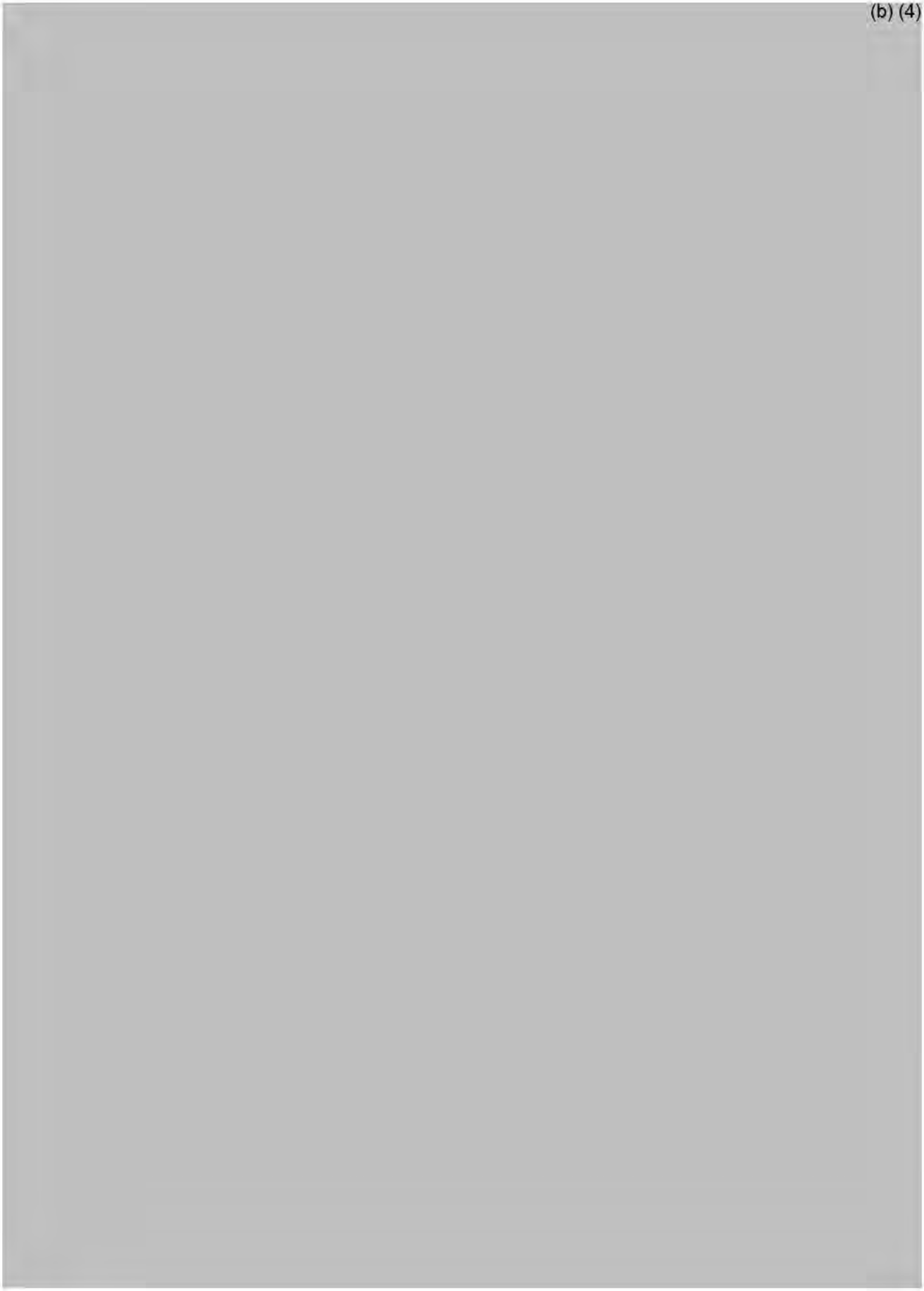
RESULTS

Carbon labeling experiments

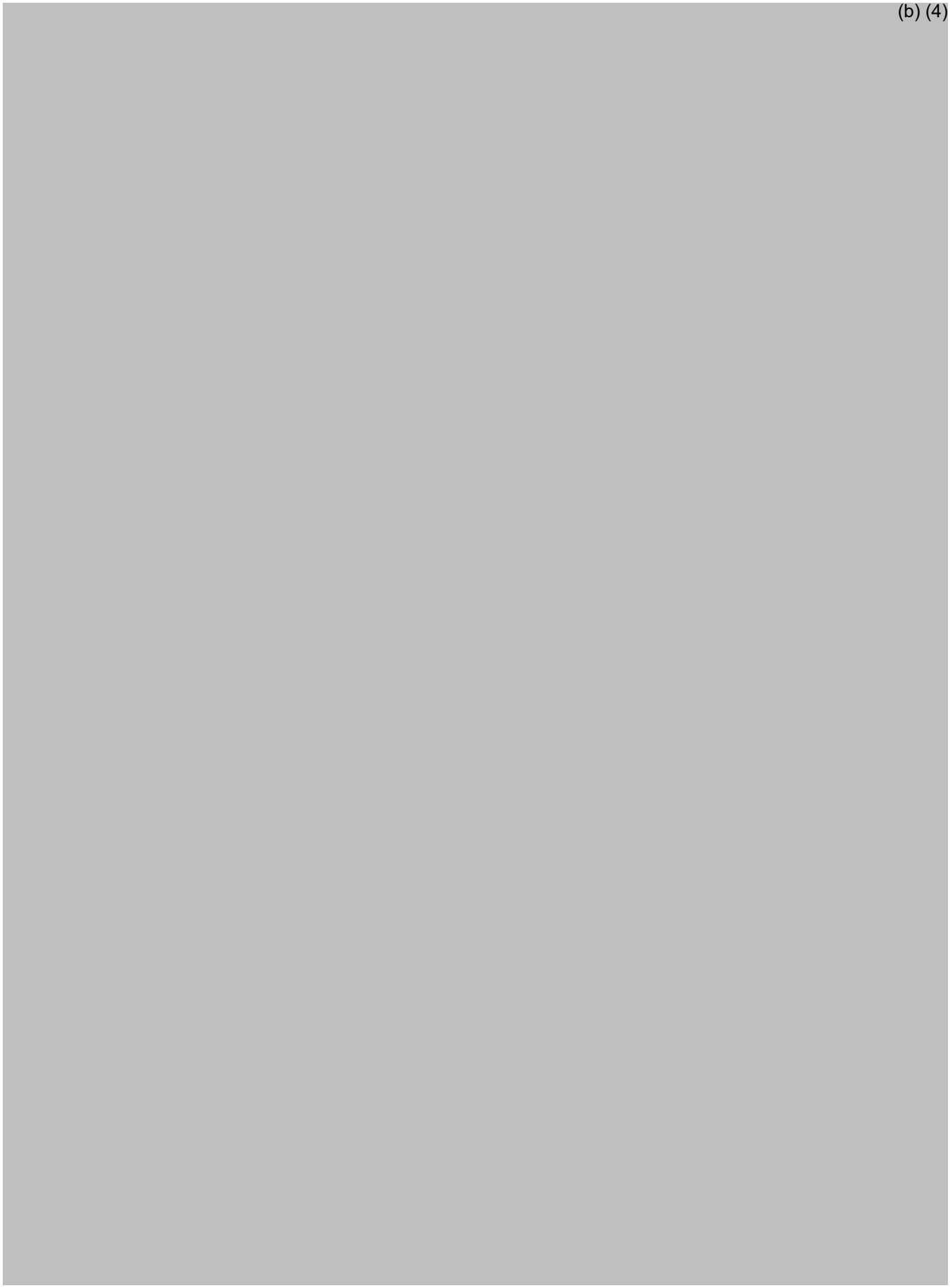
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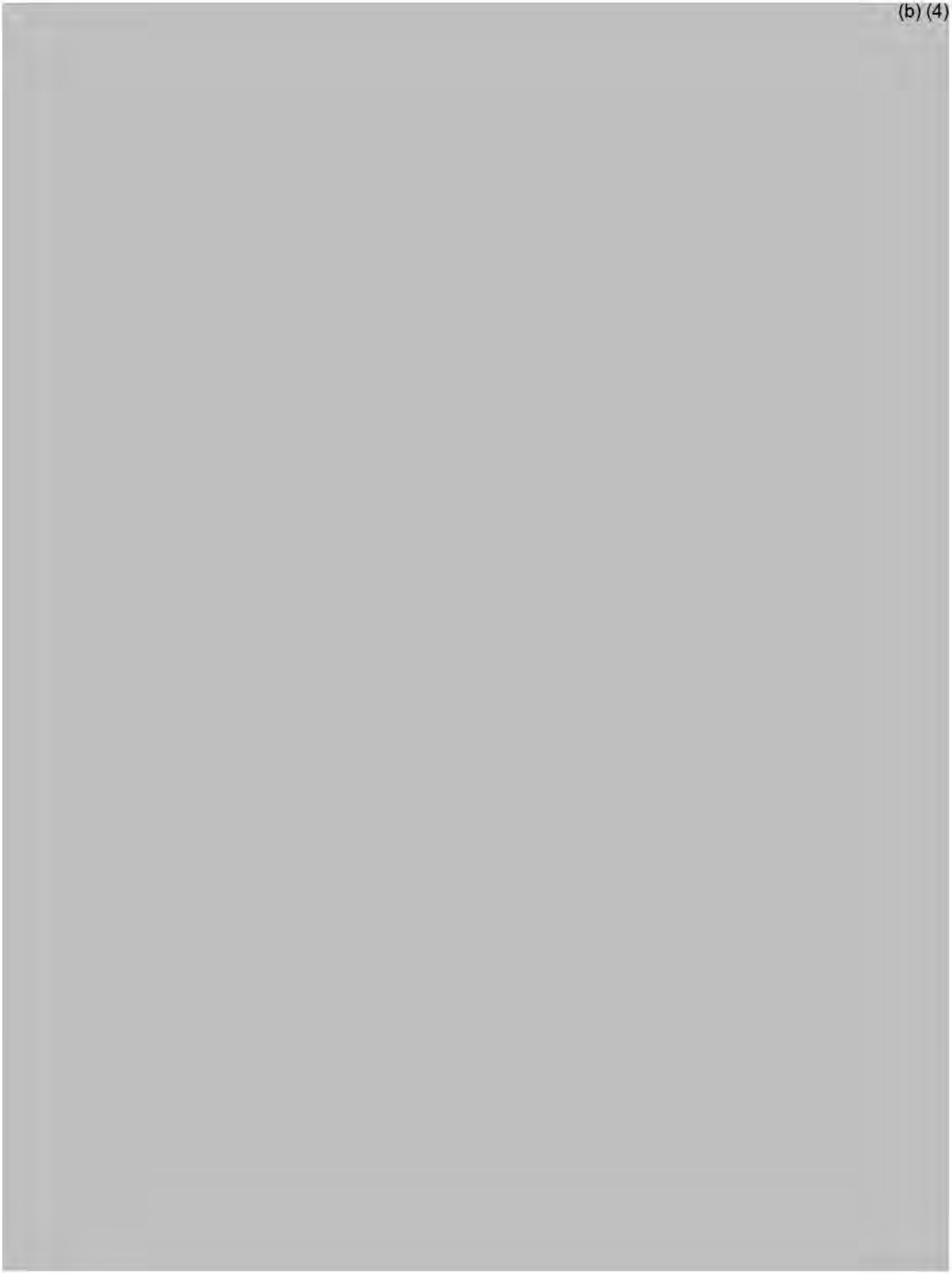

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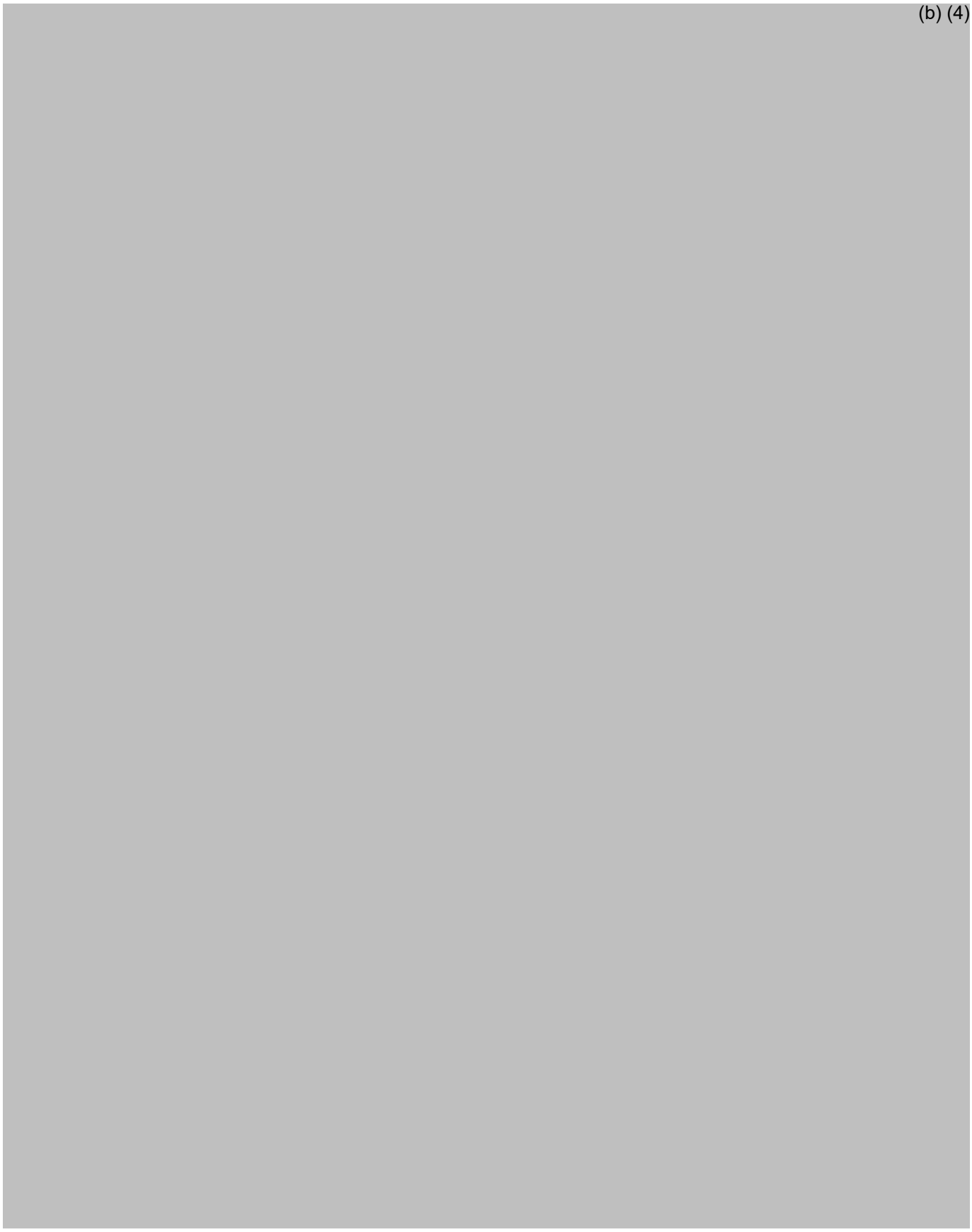
APPENDIX 2. PRE-FERMENTATION INFORMATION (CONFIDENTIAL)

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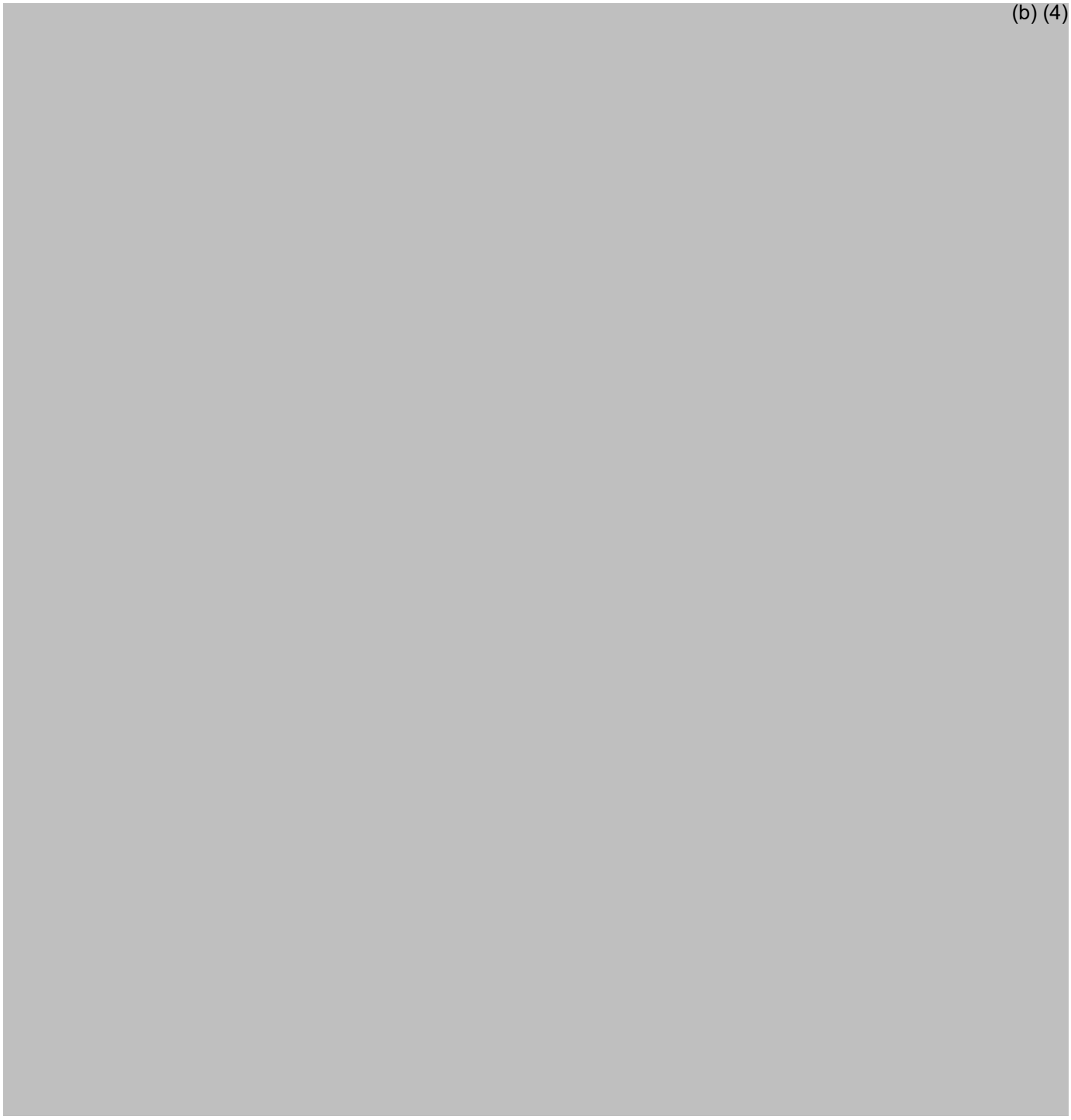


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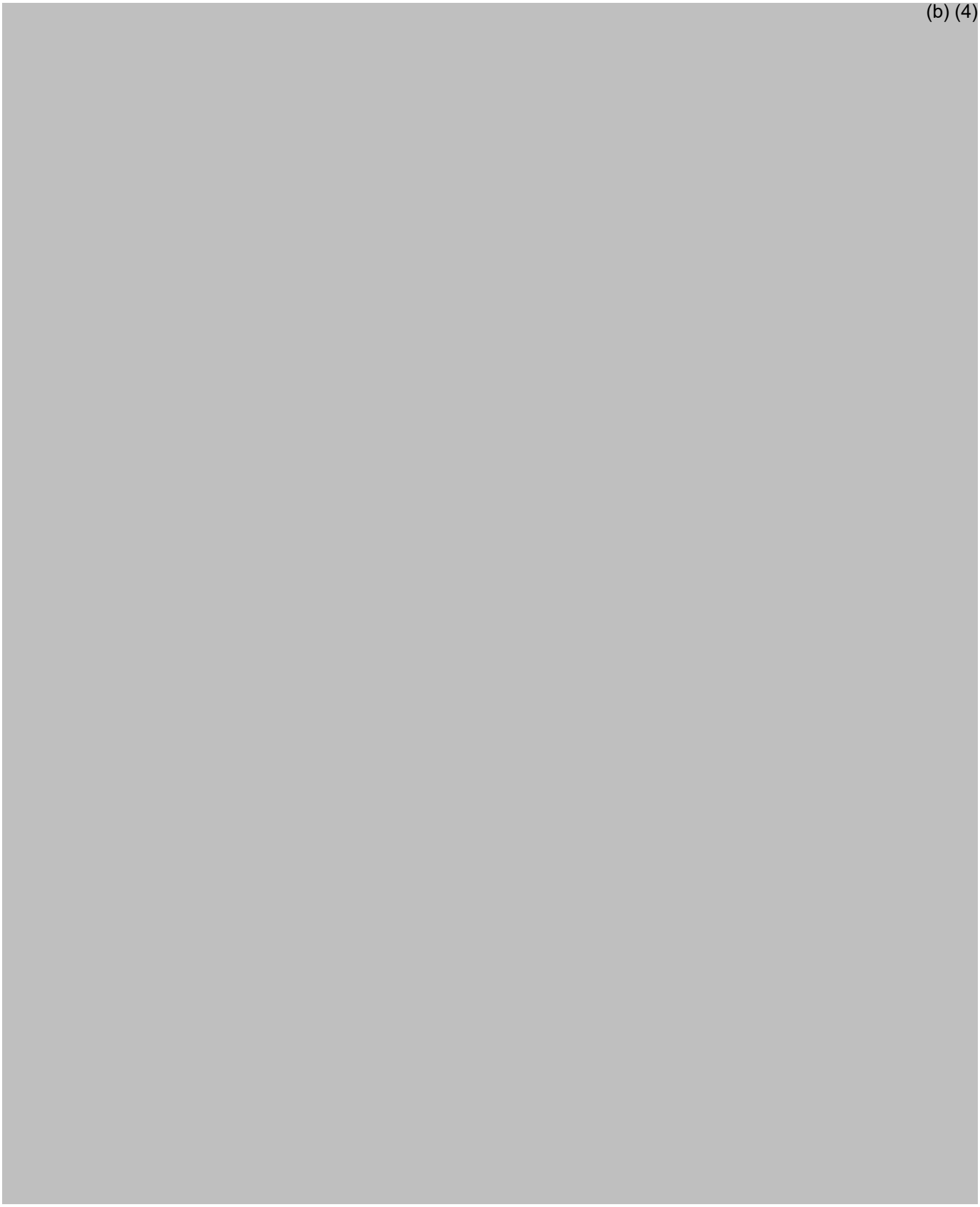
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A. CHARACTERIZATION OF THE PRODUCTION MICROORGANISM

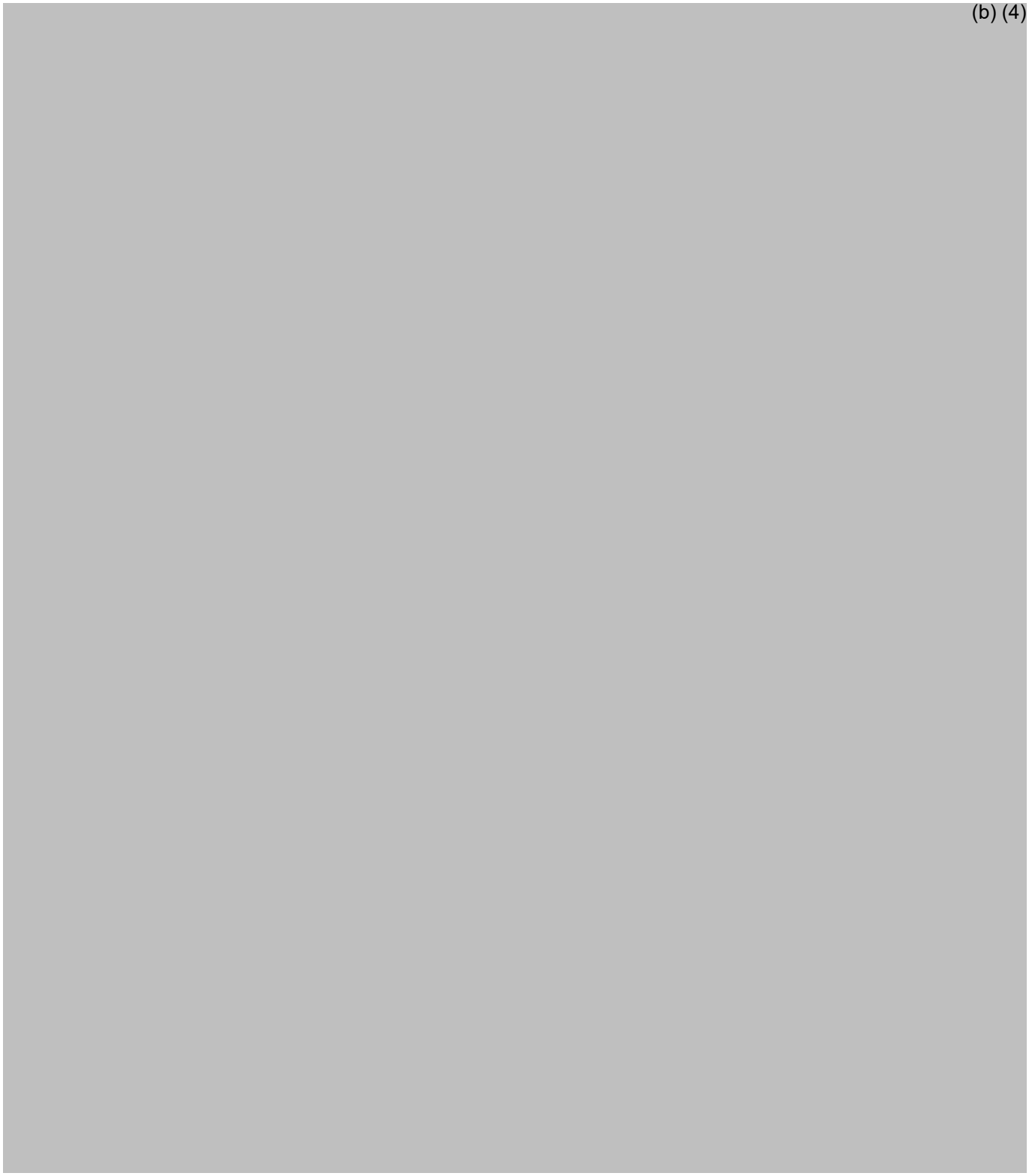
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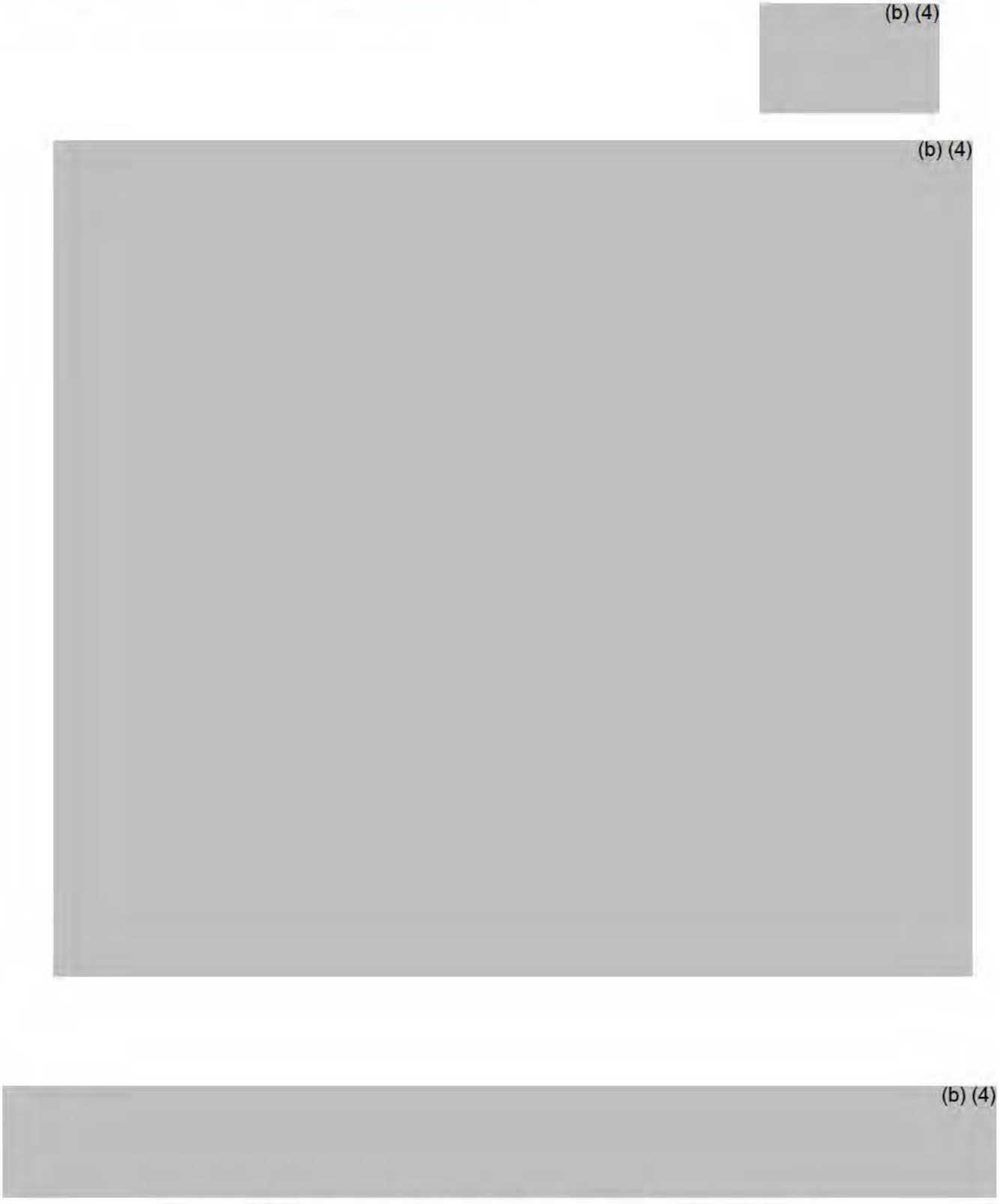
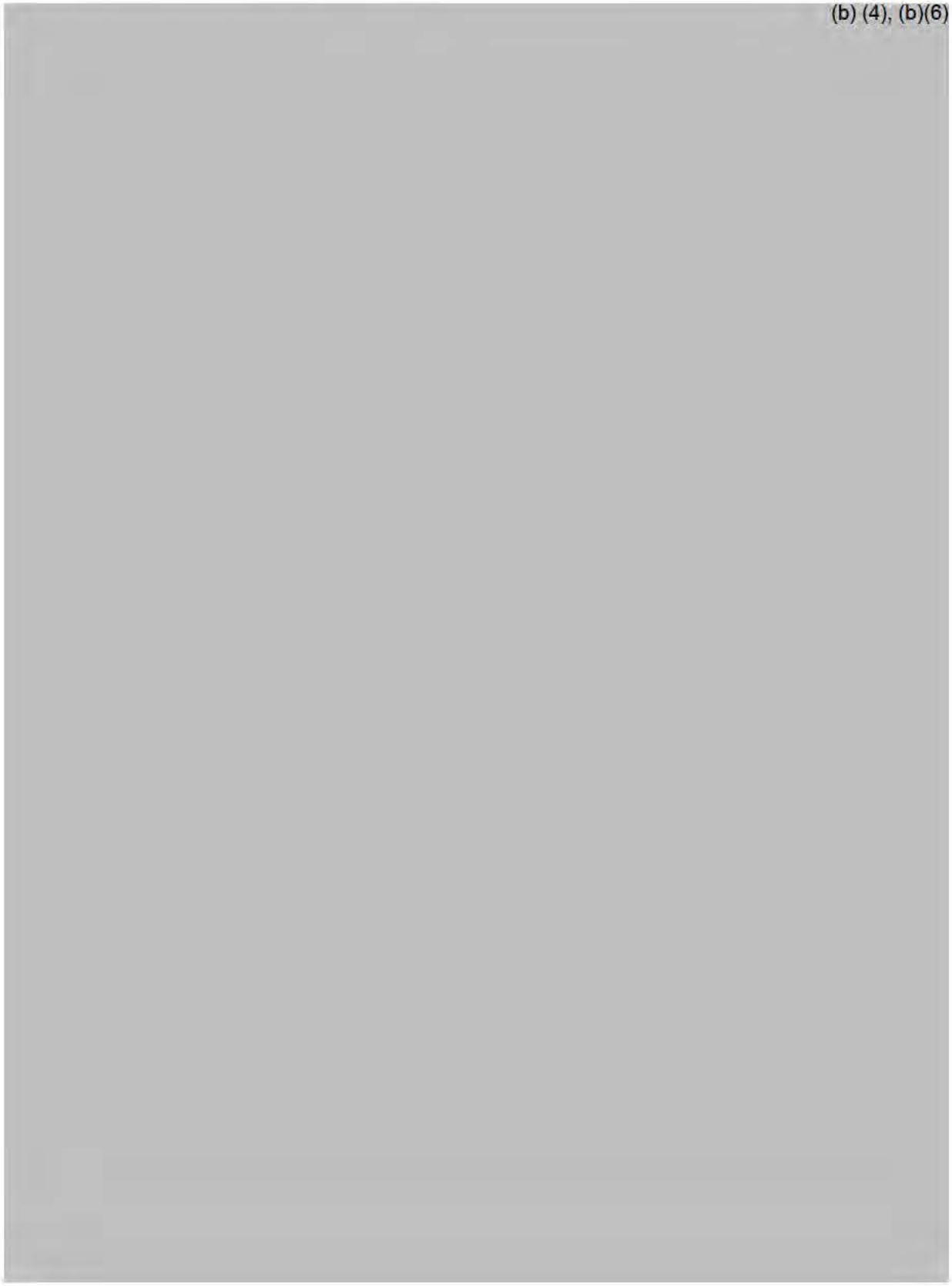
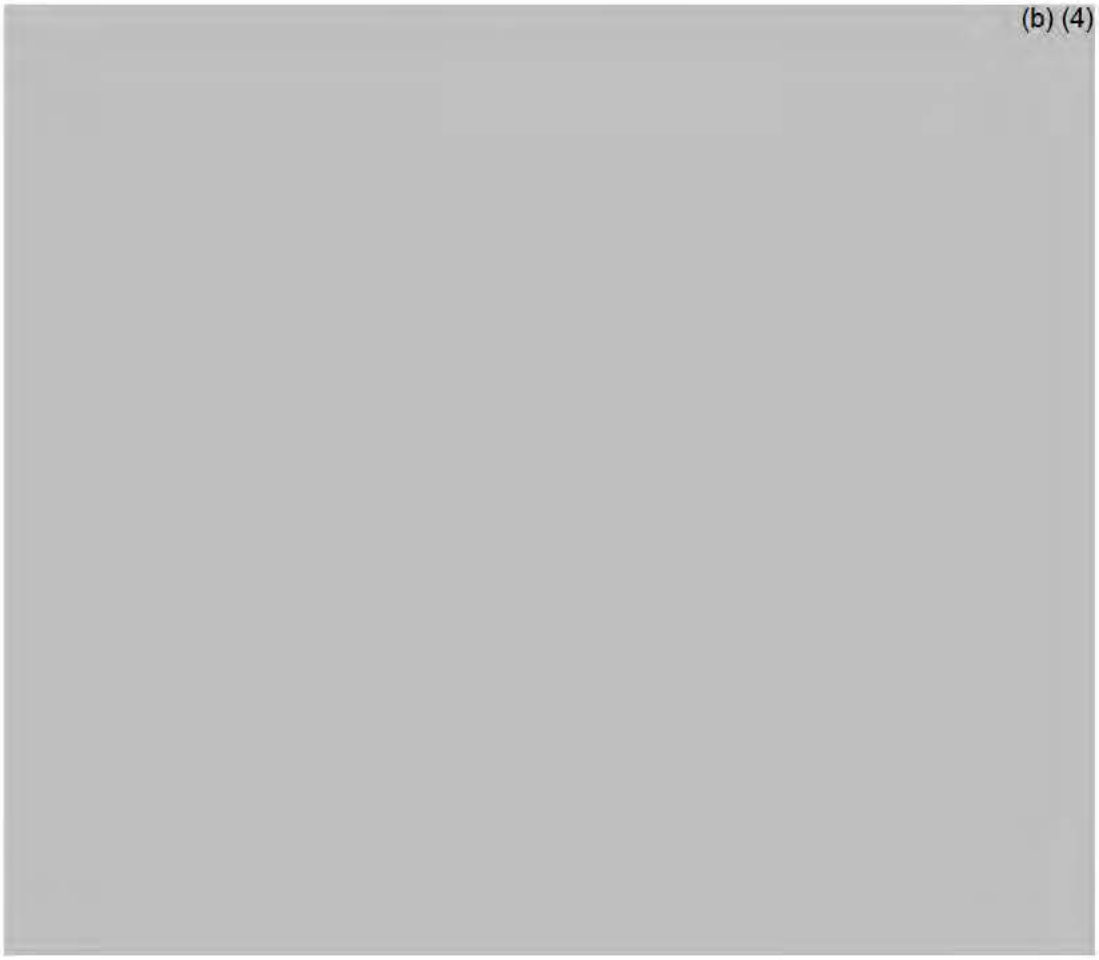


Figure A.3.1. Certificate of deposition (*C. glutamicum* KCCM 80346)


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Figure A.3.2. 16s rDNA sequence analysis of *C. glutamicum* KCCM 80346

B. INFORMATION OF DRIED L-TRYPTOPHAN FERMENTATION PRODUCT PRODUCING STRAIN, *CORYNEBACTERIUM GLUTAMICUM* KCCM 80346

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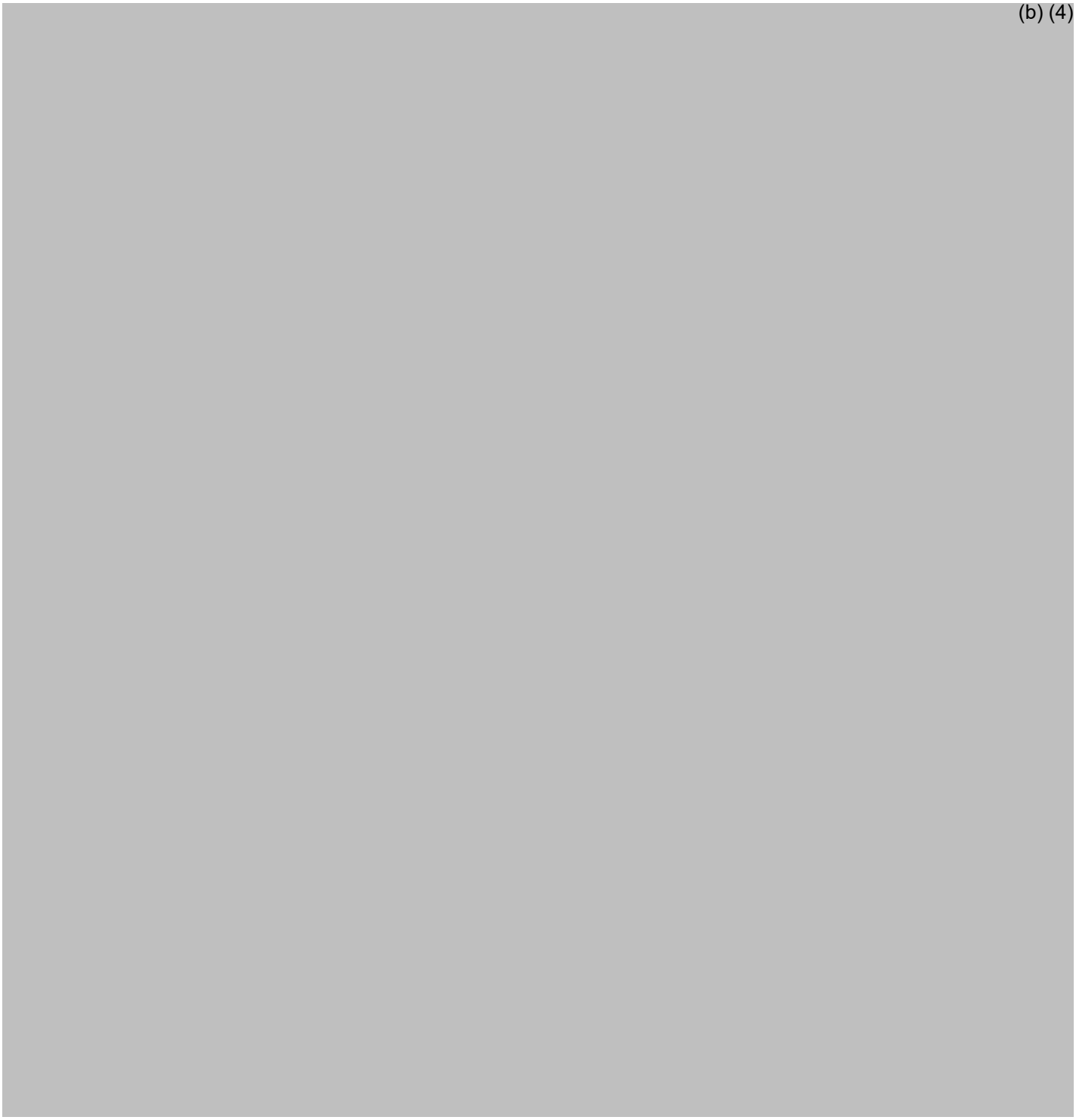
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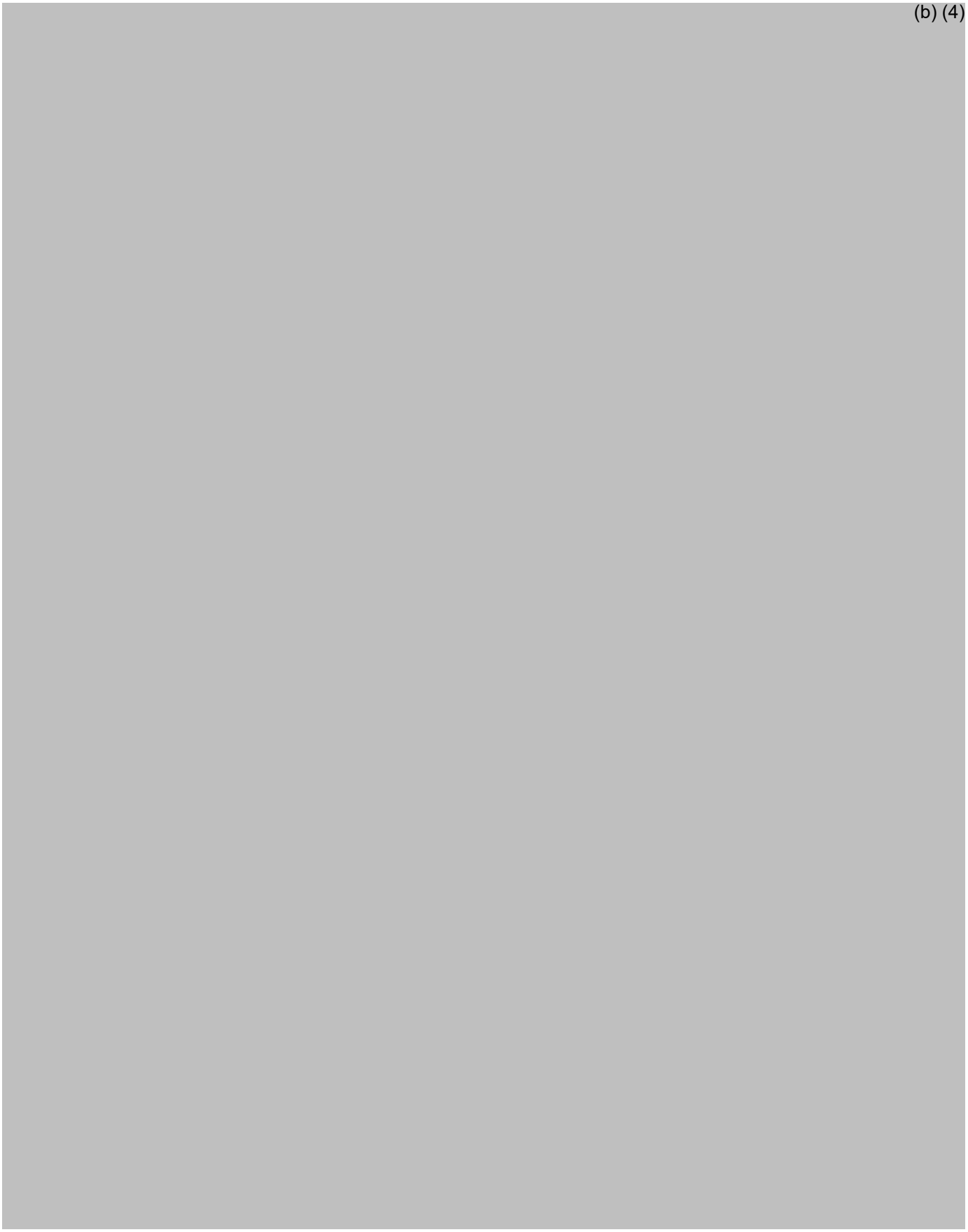
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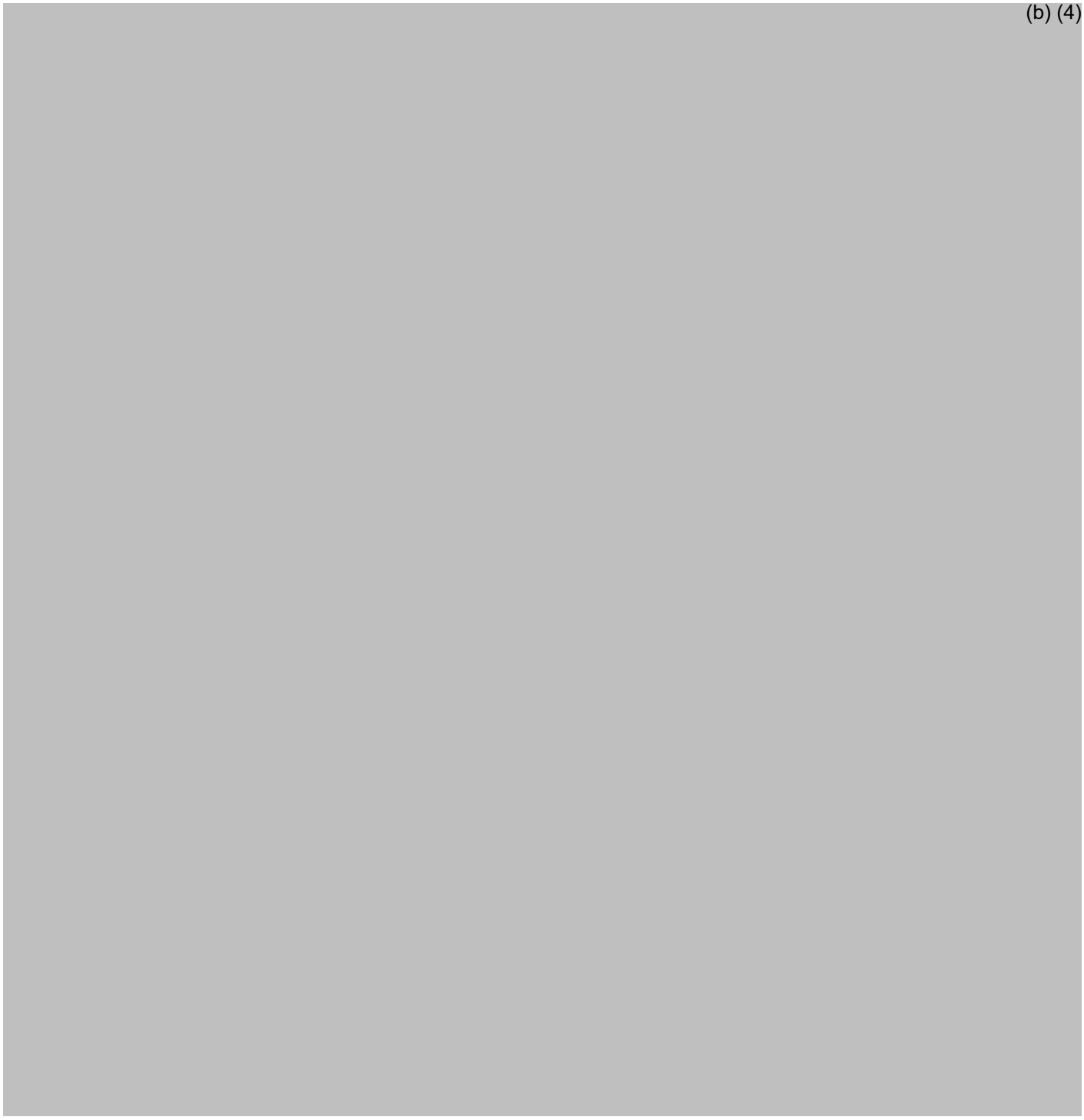
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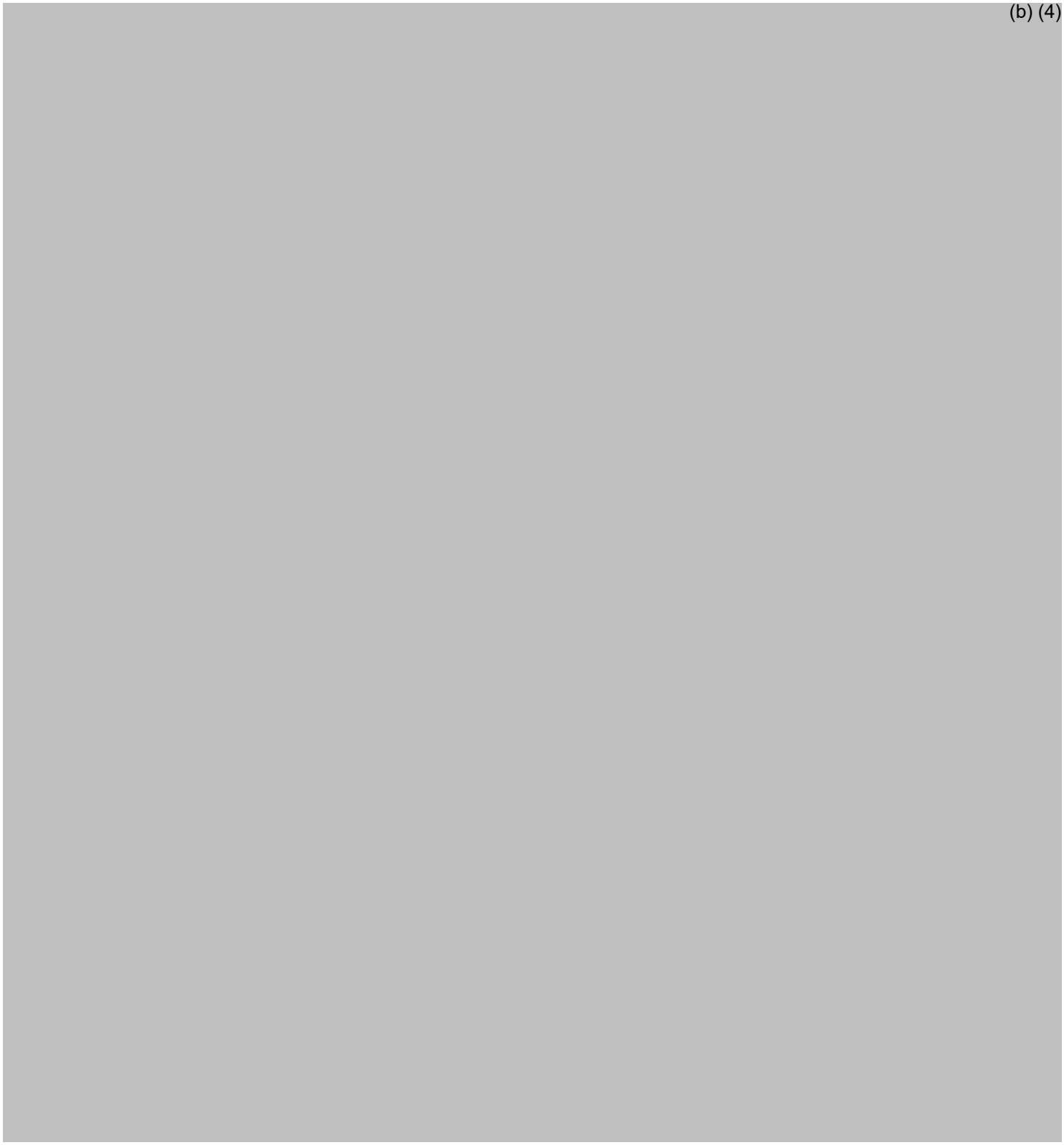
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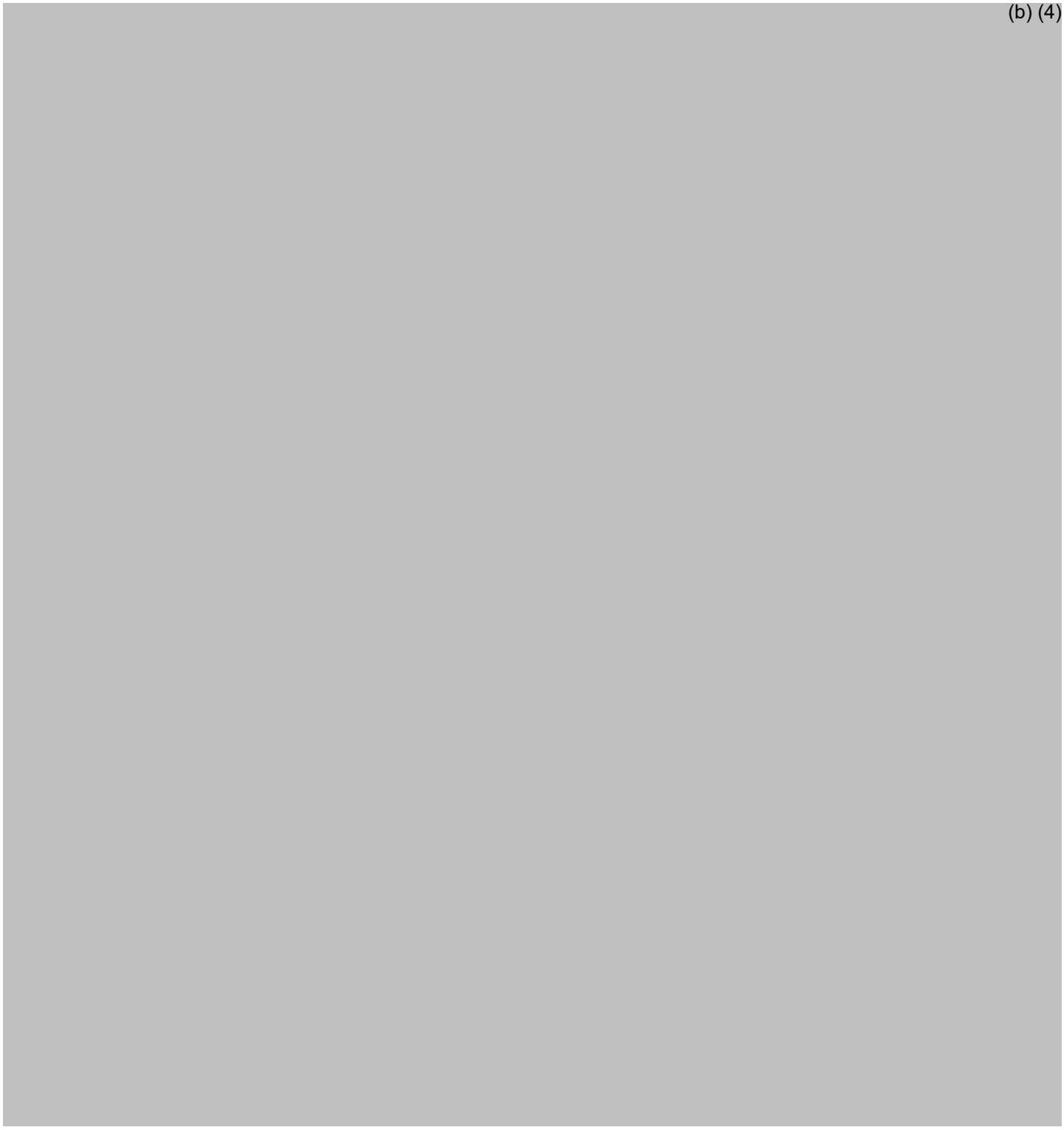
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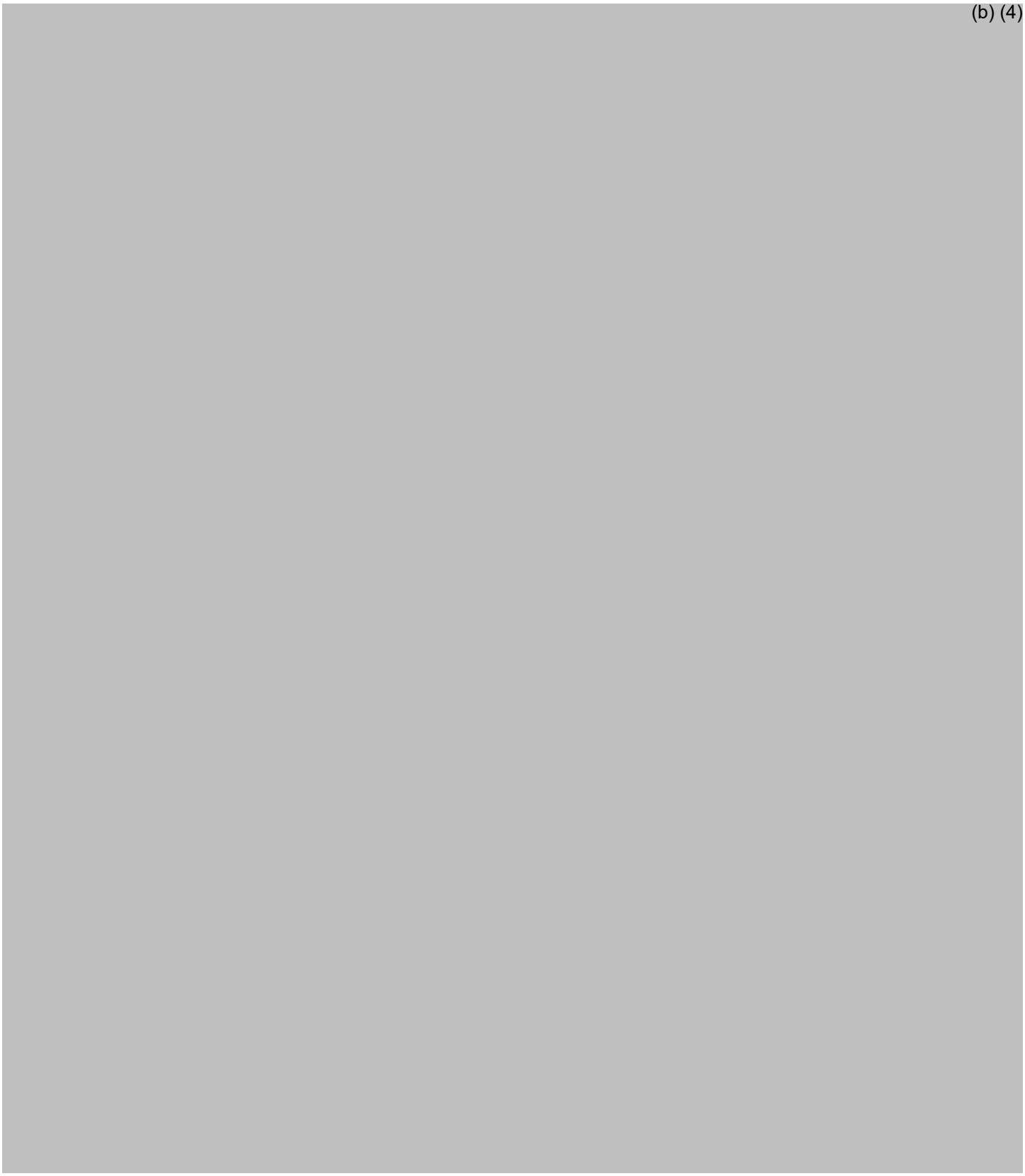
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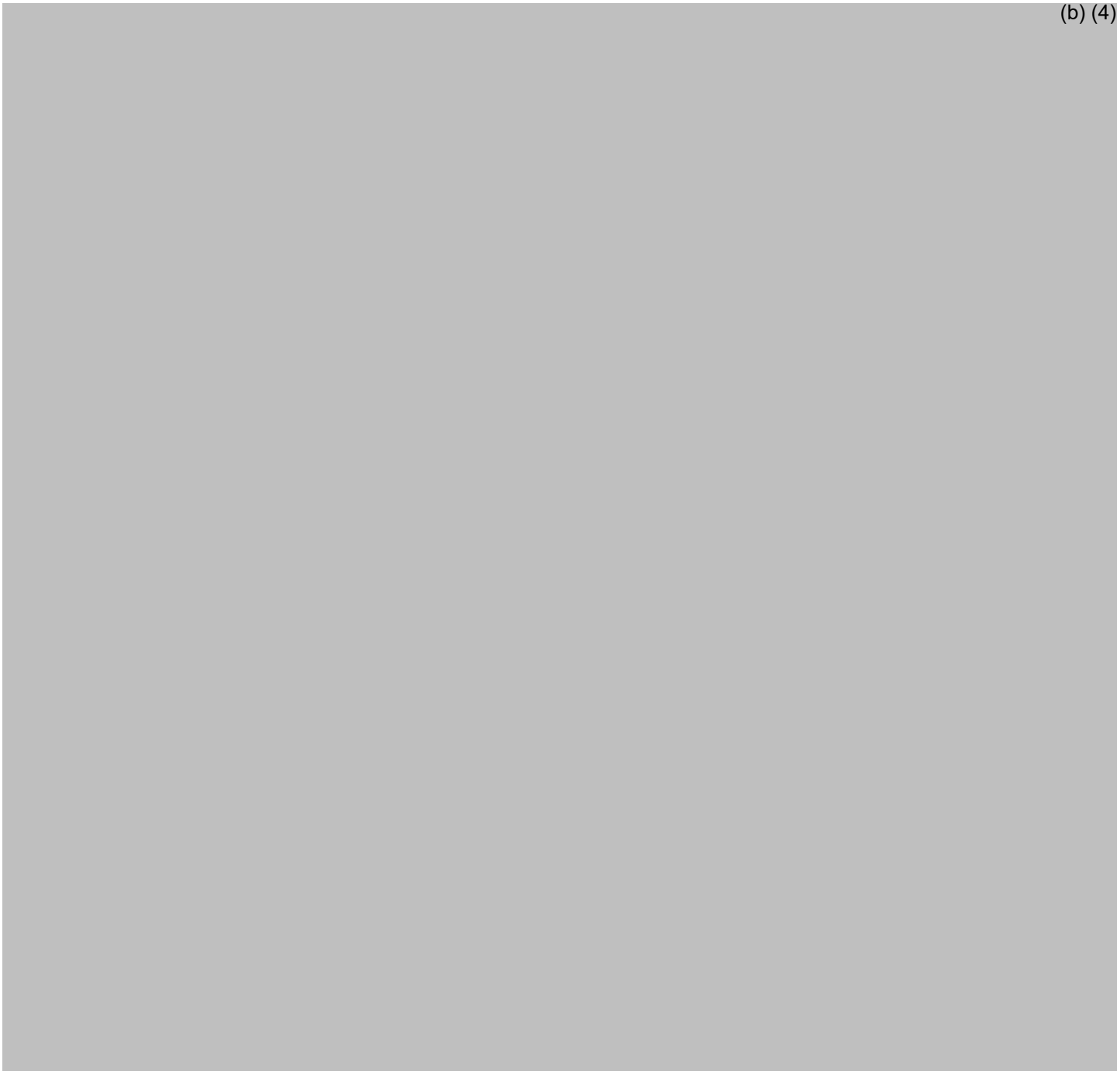
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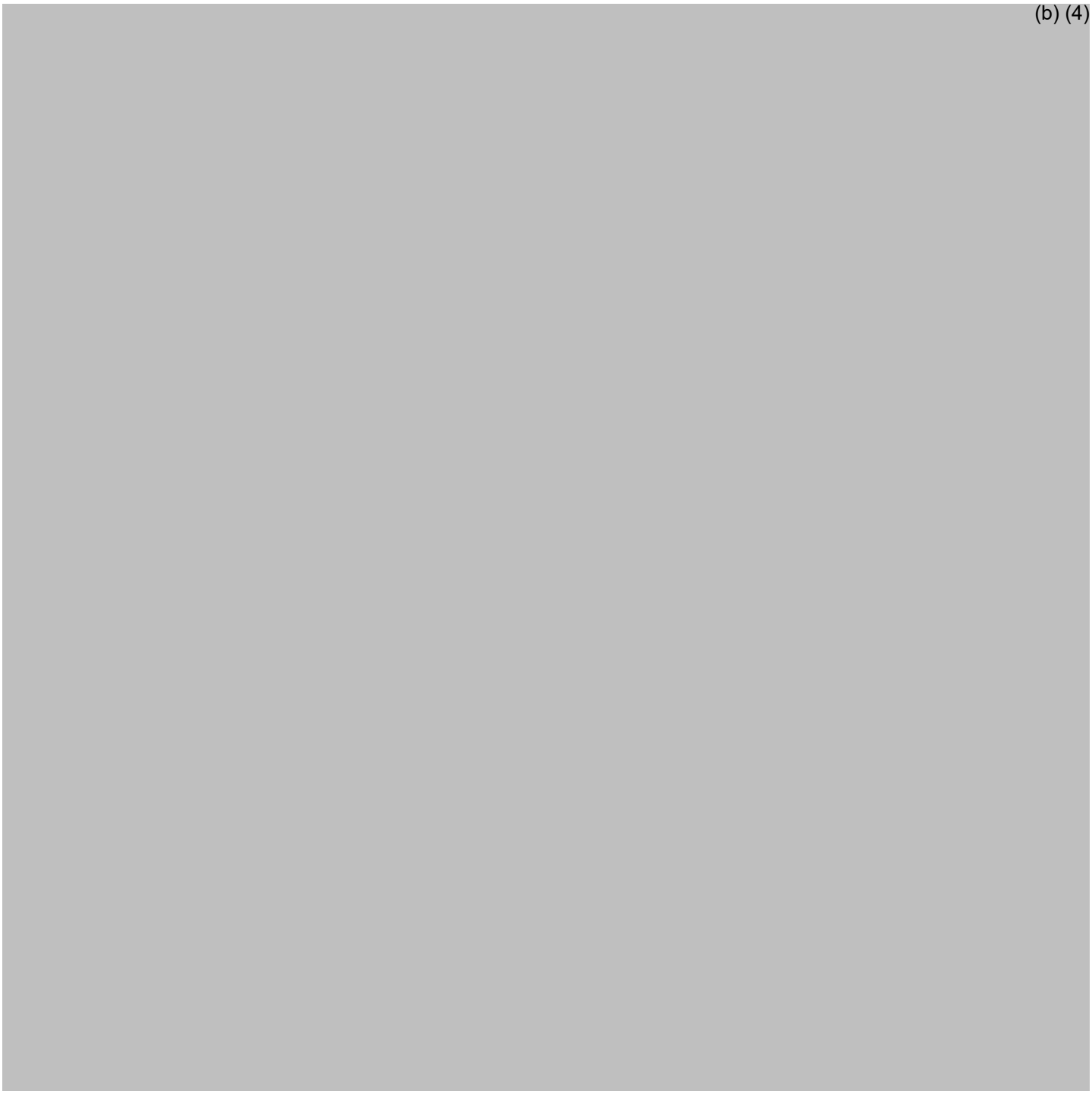
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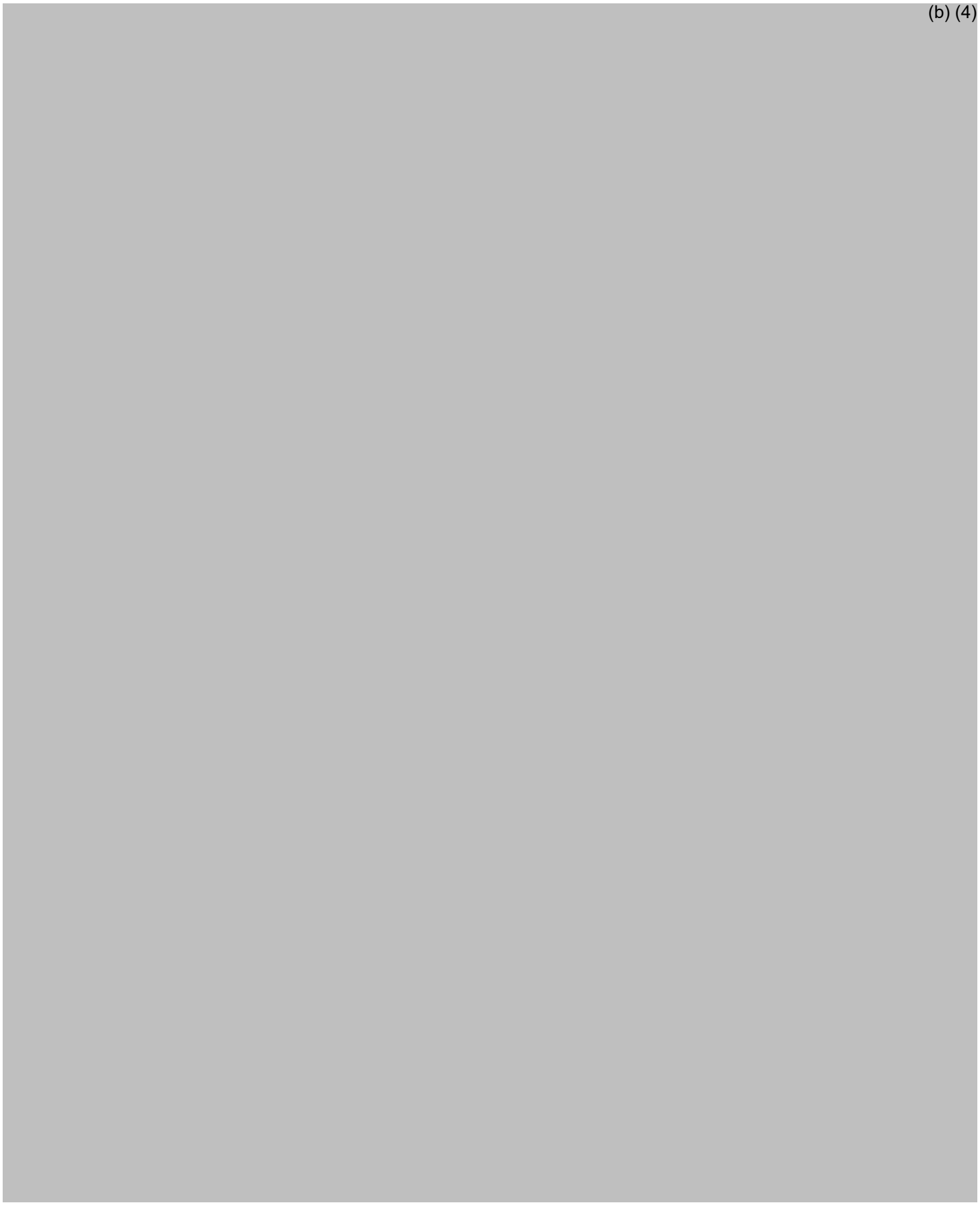
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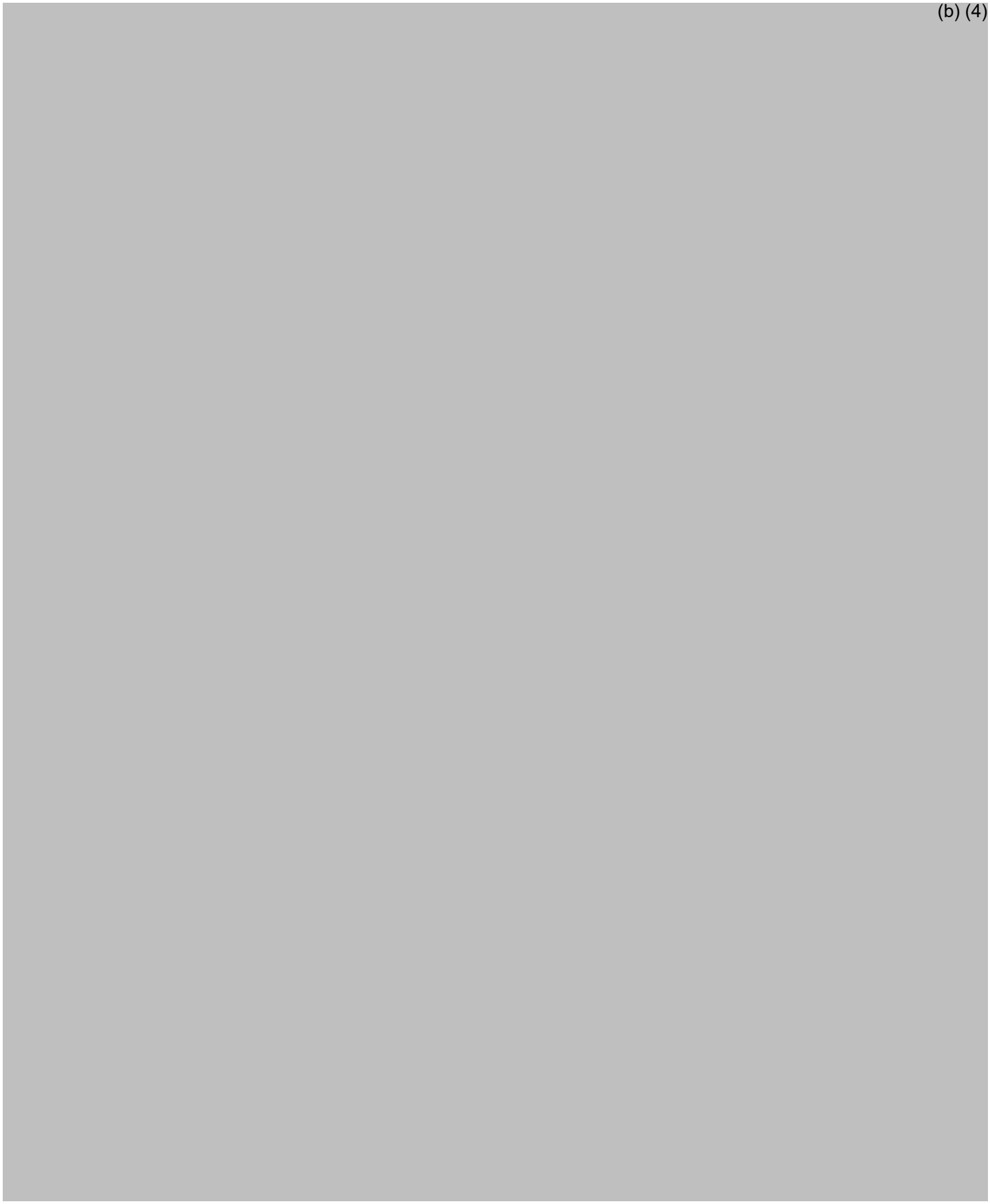
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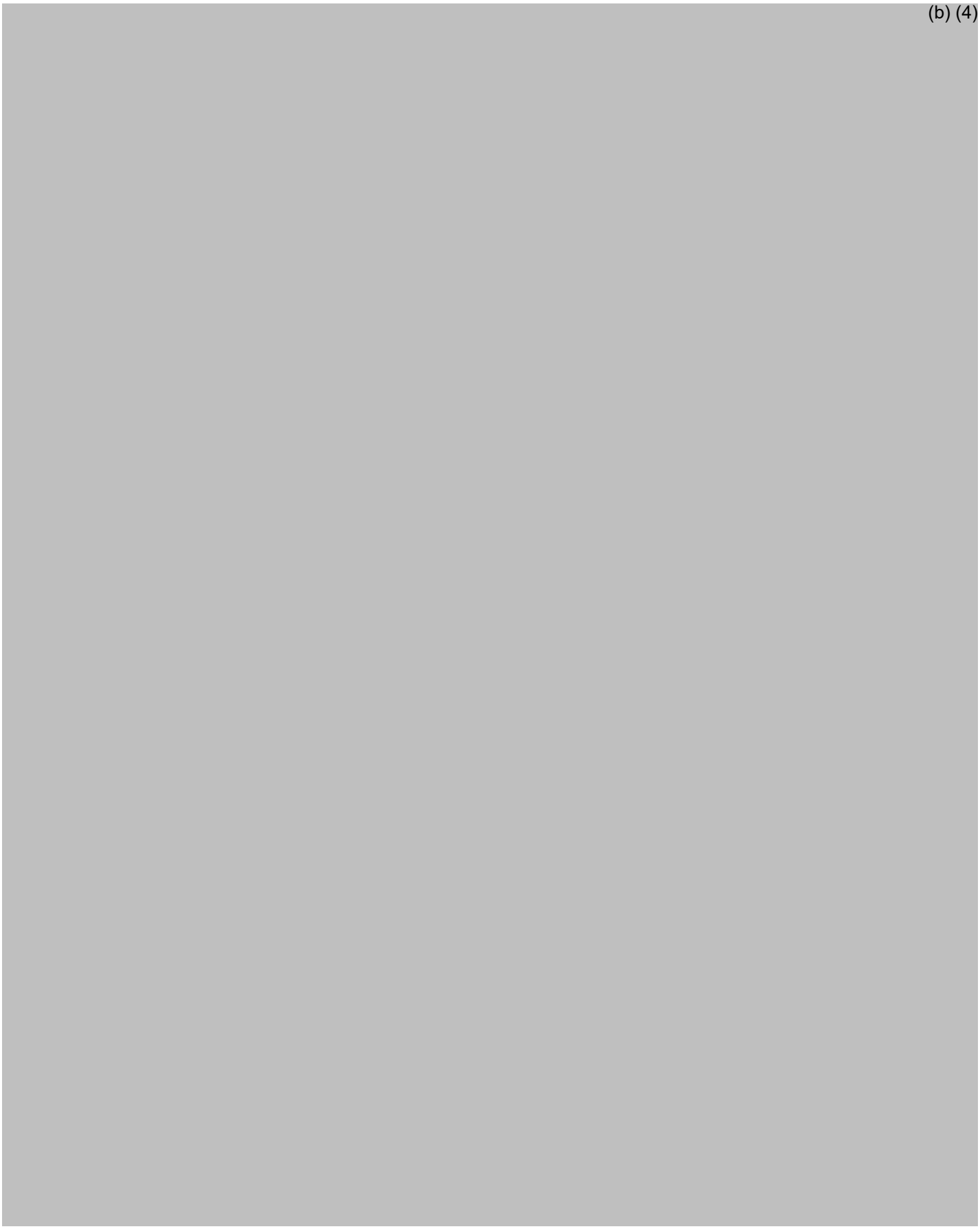
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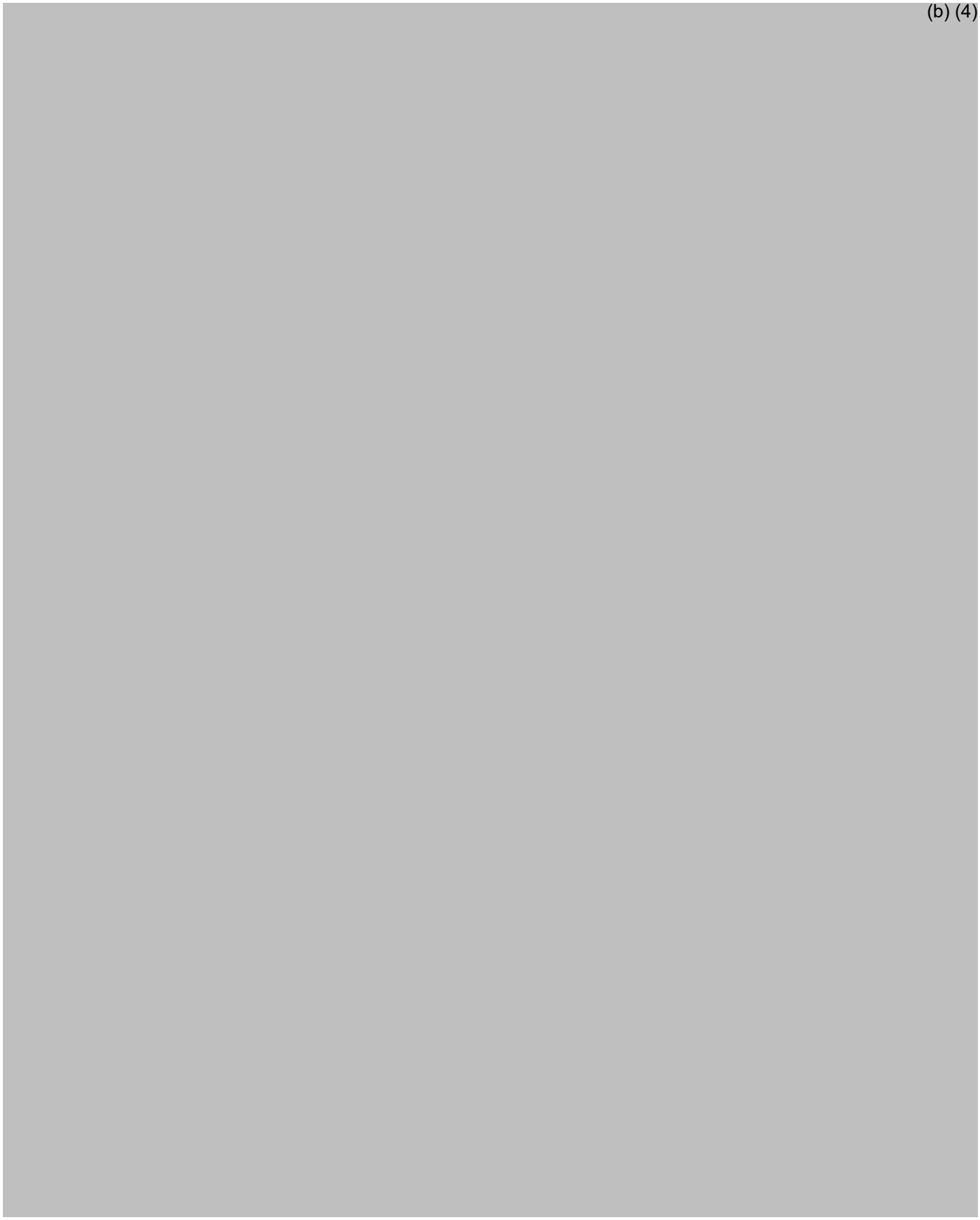
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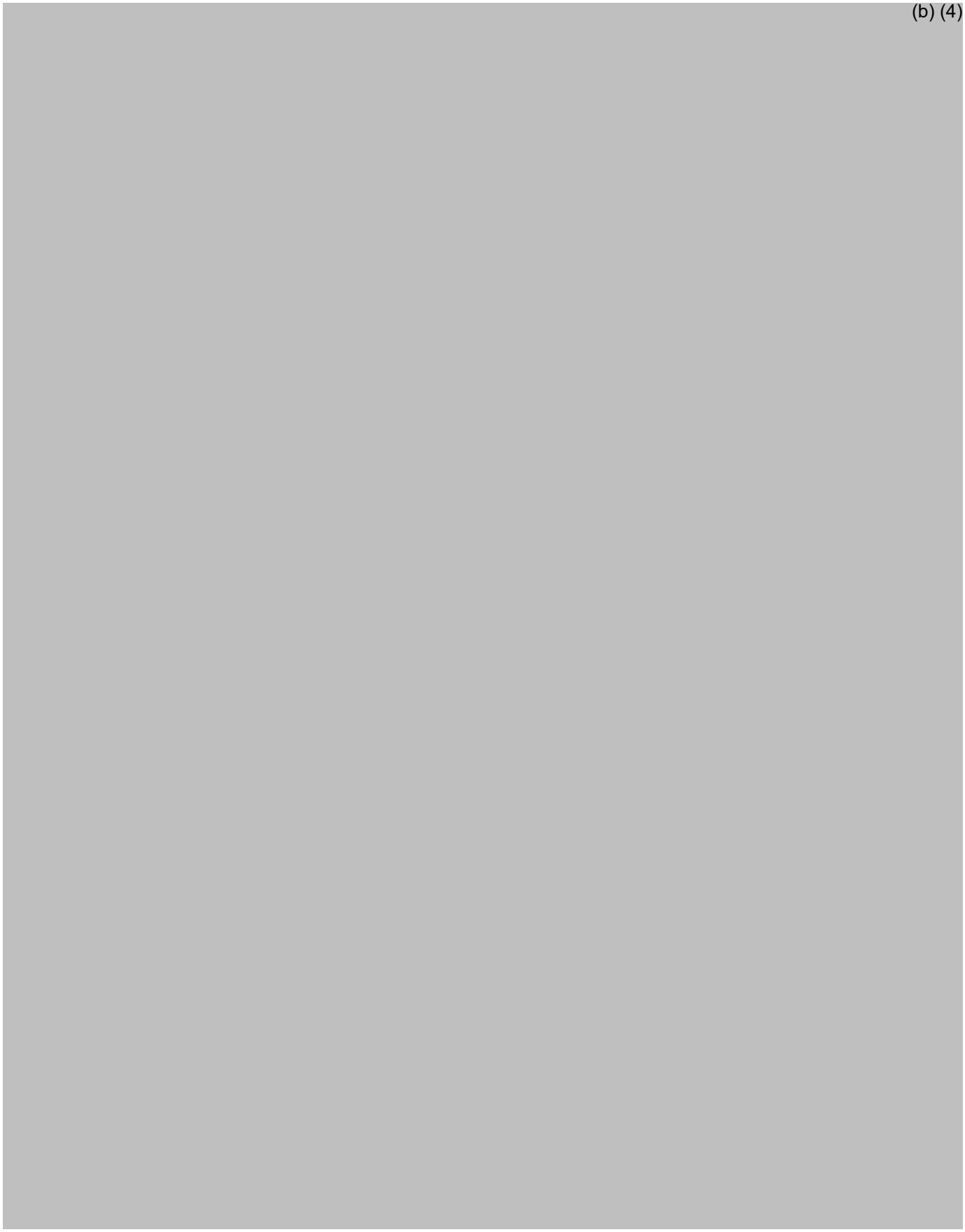
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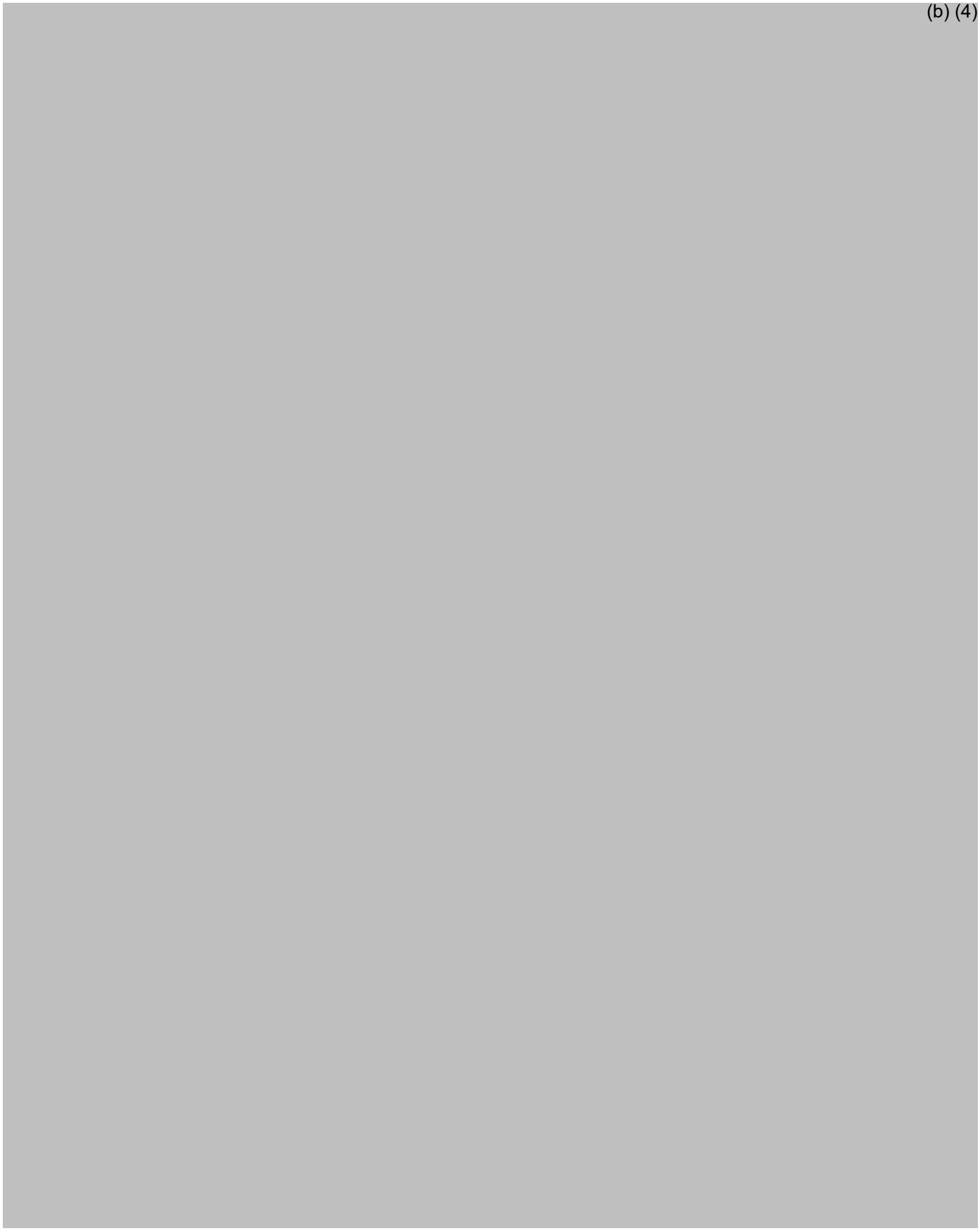
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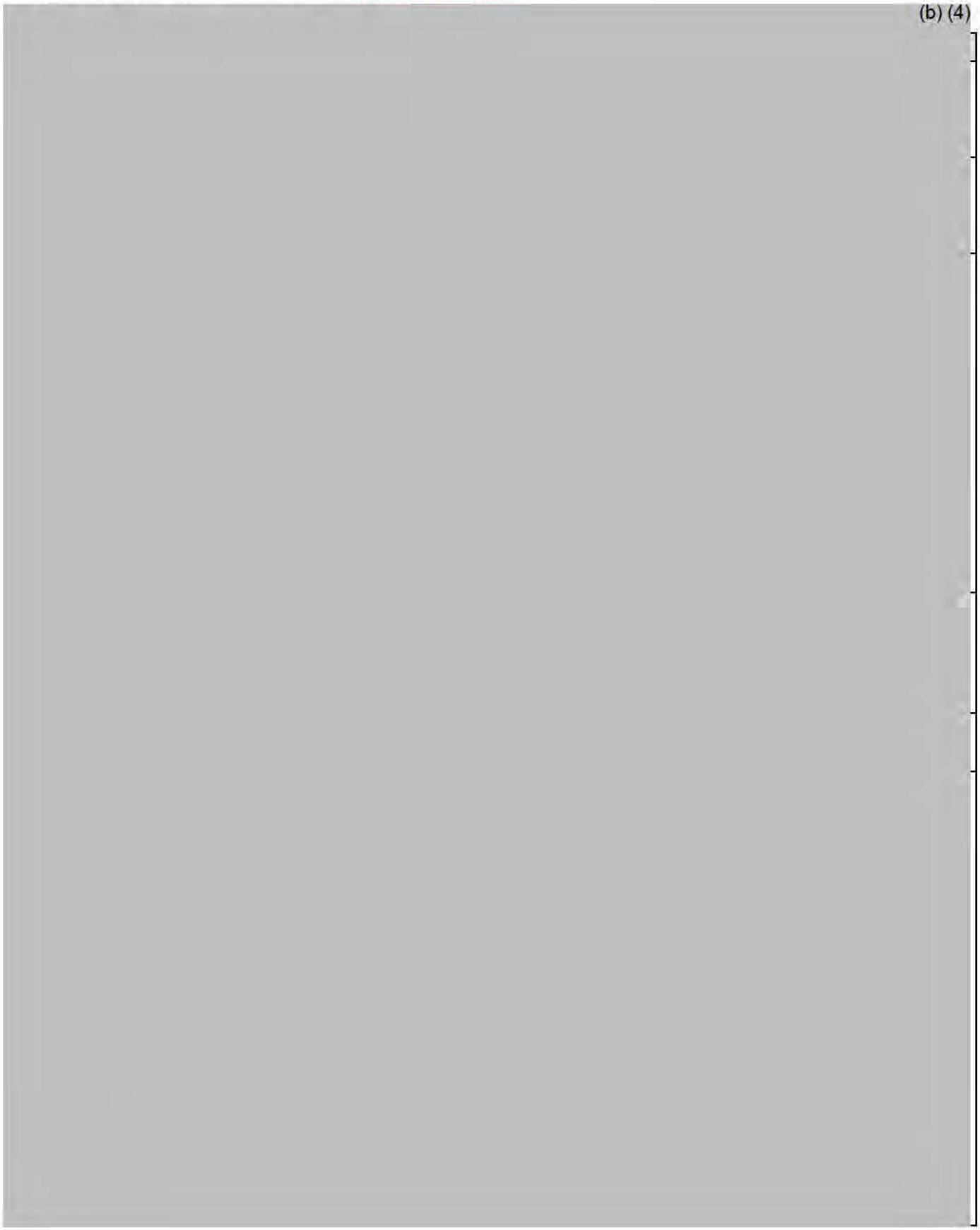
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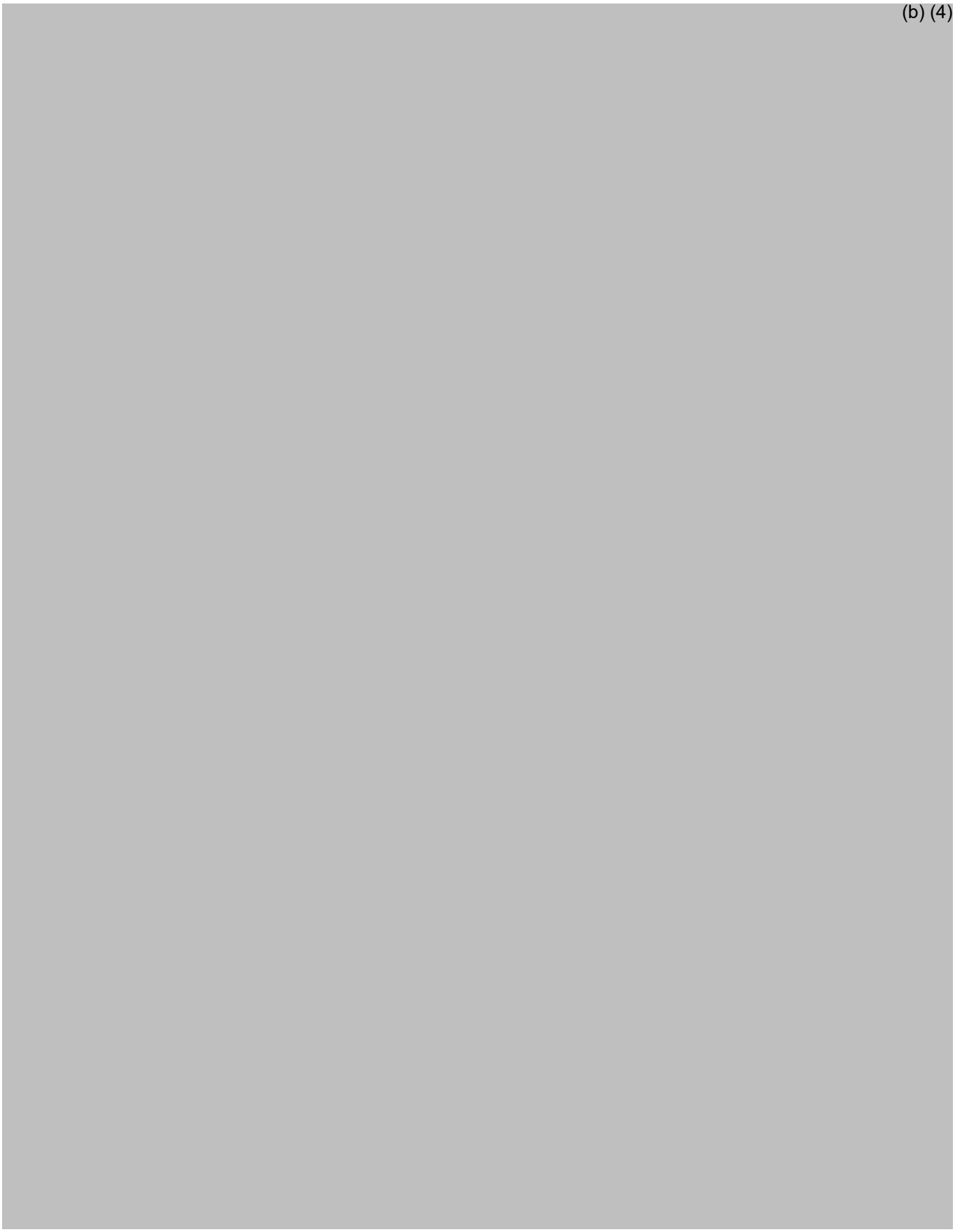


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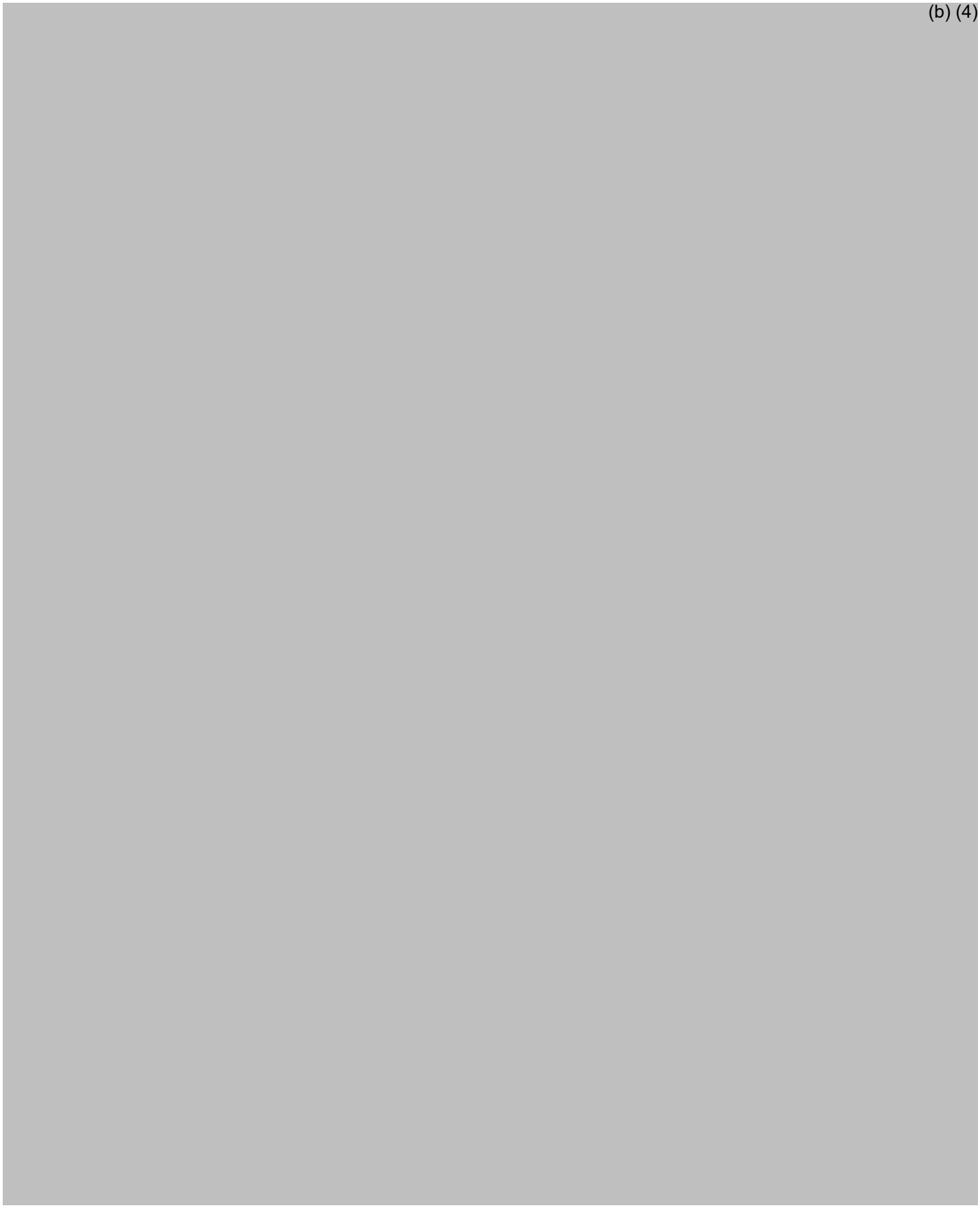
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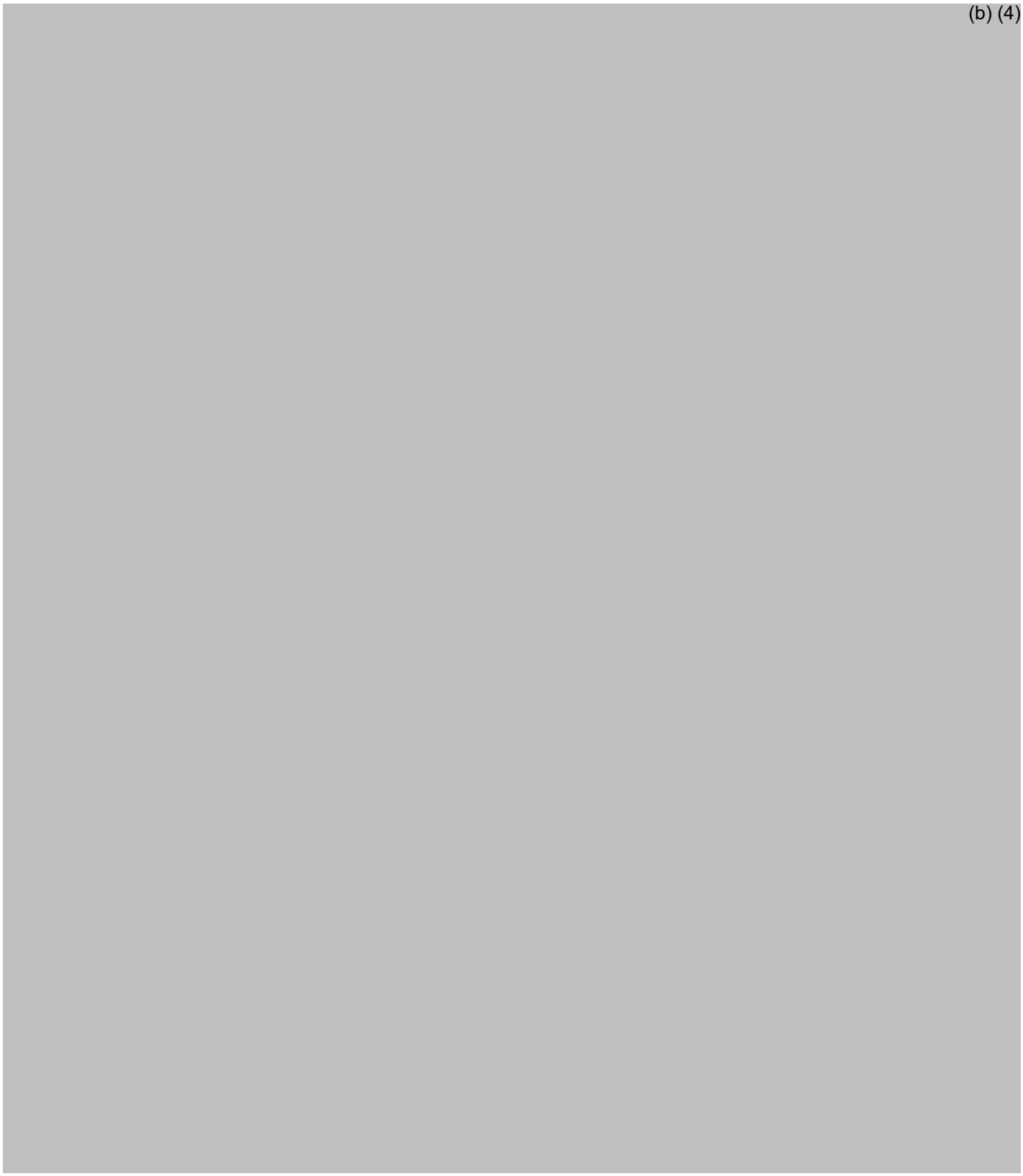
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D. LIST OF ATTACHMENTS

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E. LIST OF REFERENCES

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APPENDIX 3 - Manufacturing Process (CONFIDENTIAL)

(b) (4)

[redacted]

1. Raw materials

(b) (4)

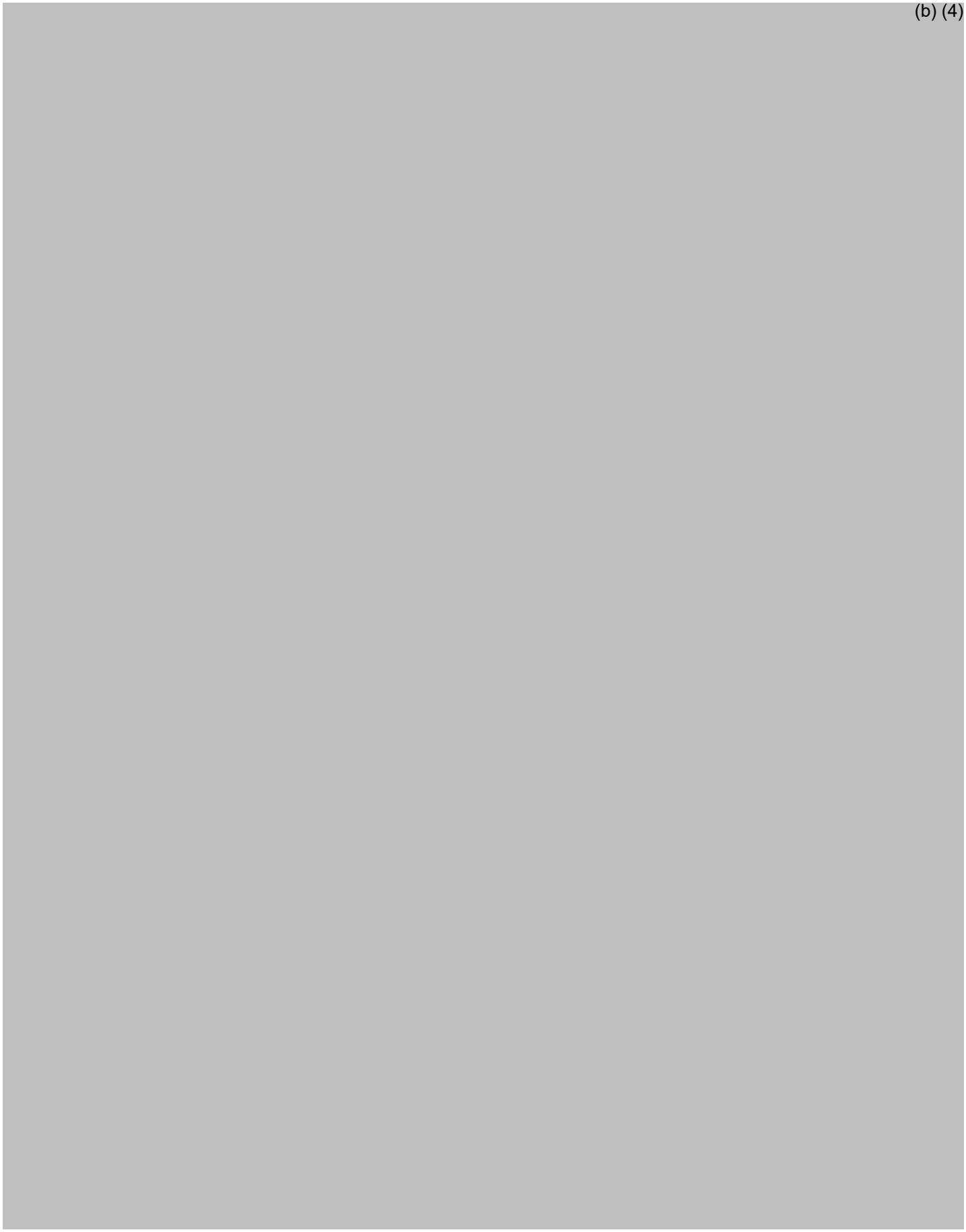
[redacted]

Appendix 3. Manufacturing Process (Confidential)

(b) (4)

[redacted]

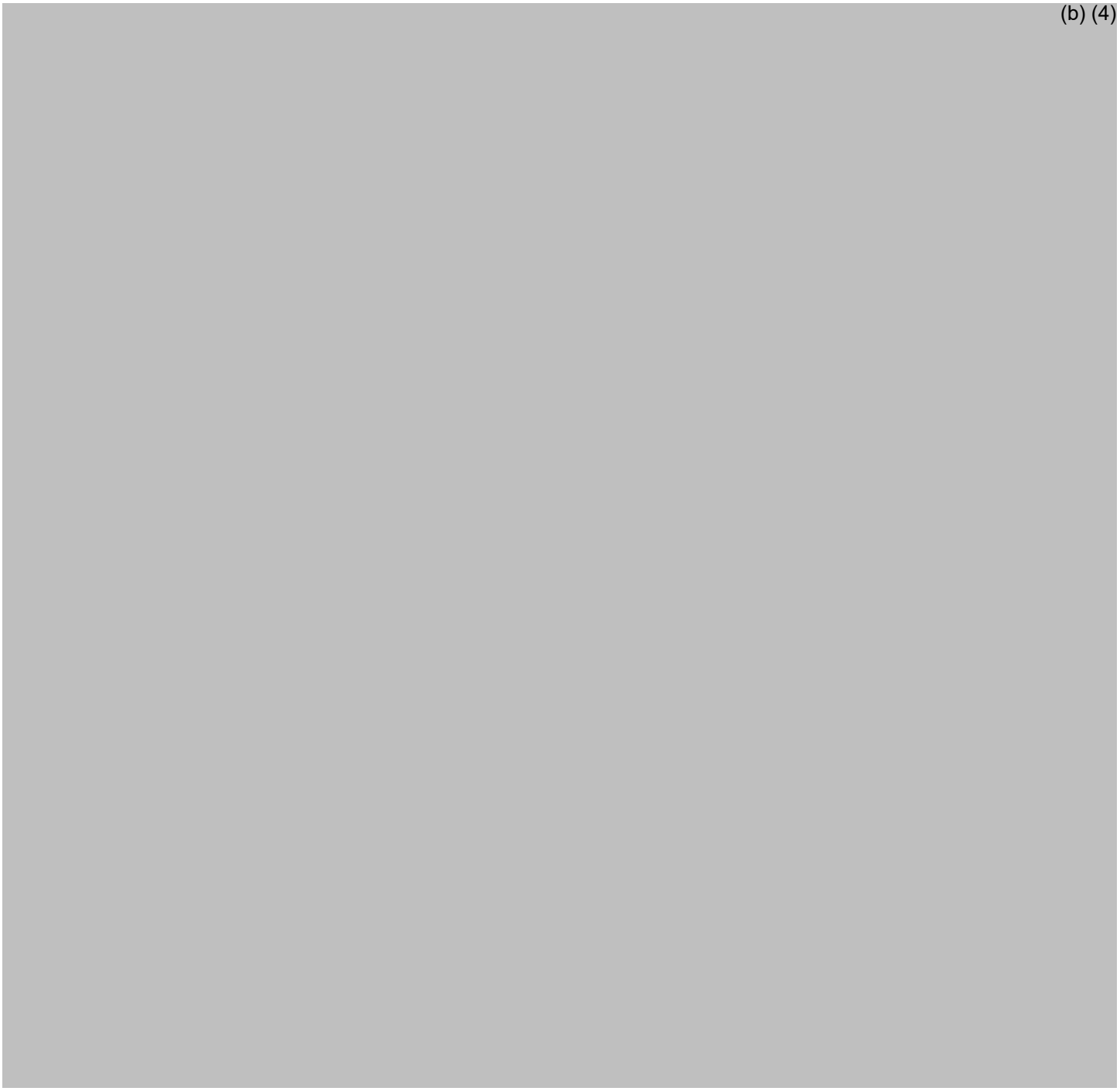
(b) (4)



5. (b) (4)

(b) (4)

(b) (4)



CONFIDENTIAL REPORT

Stability of Dried L-Tryptophan Fermentation Product (TRP Pro)

STUDY NO. (b) (4)

Version 1.0

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1. General

1.1 Title

Stability of Dried L-Tryptophan Fermentation Product (TRP Pro)

1.2 Objective

This study was conducted to observe storage stability of Dried L-Tryptophan Fermentation Product (TRP Pro) under recommended conditions.

1.3 Schedule of the study

Initiation of experiment: 14 July 2022

Termination of experiment: 20 July 2023

1.4 Test facility

Analysis & Quality, MFG, BIO, CJ CheilJedang

55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do 16495, Korea

1.5 Responsible personnel

Author	(b) (6)
Analyst	
Report approved by	

2. Materials and Methods

2.1 Information of test sample

1) Sample: Dried L-Tryptophan Fermentation Product (TRP Pro)

- L-tryptophan (dry base): not less than (b)

- Moisture: not more than (b)

2) Batch number: (b) (4)

2.2 Storage condition

(b) (4)

2.3 Analysis method

1) Content of L-tryptophan: HPLC

Parameter	Condition
System	(b) (4)
Detector	
Column	
Column temperature	
Mobile phase	
Flow rate of mobile phage	
Sample temperature	
Injection volume	
Concentration of sample and standard solution	

2) Moisture: Loss on drying (AOAC 934.01)

3. Results

The CoAs (Certificate of Analysis) are attached in the Appendix.

Table 1. General condition (25°C / 60% RH)

Test items	Specification	Batch No.	Initial	1 month	2 months	3 months	4 months	5 months	6 months	9 months	12 months
L-tryptophan (% dry matter basis)	≥ 60	(b) (4)									(b) (4)
Moisture (%)	≤ 5										

Table 2. Accelerated condition (40°C / 75% RH)

Test items	Specification	Batch No.	Initial	1 month	2 months	3 months	4 months	5 months	6 months
L-tryptophan (% dry matter basis)	≥ 60	(b) (4)							(b) (4)
Moisture (%)	≤ 5								

4. Appendix_Certificate of analysis

A. L-tryptophan (Lot number: (b) (4)

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Certificate of analysis

Certificate No.	2022-PR-185	Receipt No.	2022-AN-179
Client	-	Date of Receipt	2022.07.14
Client Name	-	Date of Test	2022.07.22.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_init		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) °C, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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Certificate of analysis

Certificate No.	2022-PR-188	Receipt No.	2022-AN-182
Client	-	Date of Receipt	2022.08.17
Client Name	-	Date of Test	2022.08.20.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_1m		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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Certificate of analysis

Certificate No.	2022-PR-197	Receipt No.	2022-AN-191
Client	-	Date of Receipt	2022.09.20
Client Name	-	Date of Test	2022.09.22
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_2m		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

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Certificate of analysis

Certificate No.	2022-PR-206	Receipt No.	2022-AN-200
Client	-	Date of Receipt	2022.10.12.
Client Name	-	Date of Test	2022.10.18.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_3m		
Manuf. Date	2021.09.30		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) °C, Relative Humidity : (10~80) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
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Certificate of analysis

Certificate No.	2023-PR-196	Receipt No.	2023-AN-166
Client	-	Date of Receipt	2022.11.14.
Client Name	-	Date of Test	2022.11.16.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_4m		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %
* The resu4lts shown in this test report refer only to the sample tested unless otherwise stated.

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Certificate of analysis

Certificate No.	2023-PR-205	Receipt No.	2023-AN-175
Client	-	Date of Receipt	2022.12.12.
Client Name	-	Date of Test	2022.12.21.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_5m		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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Certificate of analysis

Certificate No.	2023-PR-214	Receipt No.	2023-AN-184
Client	-	Date of Receipt	2023.01.18.
Client Name	-	Date of Test	2023.01.30.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_6m		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

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Certificate of analysis

Certificate No.	2023-PR-223	Receipt No.	2023-AN-193
Client	-	Date of Receipt	2023.04.19.
Client Name	-	Date of Test	2023.04.25.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_9m		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %
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Certificate of analysis

Certificate No.	2023-PR-282	Receipt No.	2023-AN-235
Client	-	Date of Receipt	2023.07.20.
Client Name	-	Date of Test	2023.08.07.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_12m		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) °C, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.
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August 29, 2023

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Certificate of analysis

Certificate No.	2022-PR-194	Receipt No.	2022-AN-188
Client	-	Date of Receipt	2022.08.17
Client Name	-	Date of Test	2022.08.20.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_1m		
Manuf. Date	2021.09.30		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

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Certificate of analysis

Certificate No.	2022-PR-203	Receipt No.	2022-AN-197
Client	-	Date of Receipt	2022.09.20
Client Name	-	Date of Test	2022.09.22
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_2m		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) °C, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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Certificate of analysis

Certificate No.	2022-PR-212	Receipt No.	2022-AN-206
Client	-	Date of Receipt	2022.10.12.
Client Name	-	Date of Test	2022.10.18.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_3m		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.
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Certificate of analysis

Certificate No.	2023-PR-202	Receipt No.	2023-AN-172
Client	-	Date of Receipt	2022.11.14.
Client Name	-	Date of Test	2022.11.16.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_4m		
Manuf. Date	2021.09.30.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.
The Test Report cannot be reproduced, except in full.

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Certificate of analysis

Certificate No.	2023-PR-211	Receipt No.	2023-AN-181
Client	-	Date of Receipt	2022.12.12.
Client Name	-	Date of Test	2022.12.21.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_5m		
Manuf. Date	2021.09.30		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.
The Test Report cannot be reproduced, except in full.

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Certificate of analysis

Certificate No.	2023-PR-220	Receipt No.	2023-AN-190
Client	-	Date of Receipt	2023.01.18.
Client Name	-	Date of Test	2023.01.30.
Client Tel	-	Use of Report	Reference test
Client Address	-		

Test Sample	L-tryptophan (TRP Pro)_40_6m
Manuf. Date	2021.09.30.
Lot. No	(b) (4)
Quantity (kg)	-

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.
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B. L-tryptophan (Lot number: DWFP211005)

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Certificate of analysis

Certificate No.	2022-PR-186	Receipt No.	2022-AN-180
Client	-	Date of Receipt	2022.07.14
Client Name	-	Date of Test	2022.07.22.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_init		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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Certificate of analysis

Certificate No.	2022-PR-189	Receipt No.	2022-AN-183
Client	-	Date of Receipt	2022.08.17
Client Name	-	Date of Test	2022.08.20.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_1m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
The Test Report cannot be reproduced, except in full.

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Certificate of analysis

Certificate No.	2022-PR-198	Receipt No.	2022-AN-192
Client	-	Date of Receipt	2022.09.20
Client Name	-	Date of Test	2022.09.22
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_2m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %
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October 24, 2022

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TEL : 031) 8099-2450 FAX : 031) 8099-2918

Certificate of analysis

Certificate No.	2022-PR-207	Receipt No.	2022-AN-201
Client	-	Date of Receipt	2022.10.12.
Client Name	-	Date of Test	2022.10.18.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_3m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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October 24, 2022

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Certificate of analysis

Certificate No.	2023-PR-197	Receipt No.	2023-AN-167
Client	-	Date of Receipt	2022.11.14.
Client Name	-	Date of Test	2022.11.16.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_4m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) °C, Relative Humidity : (10~80) %

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Certificate of analysis

Certificate No.	2023-PR-206	Receipt No.	2023-AN-176
Client	-	Date of Receipt	2022.12.12.
Client Name	-	Date of Test	2022.12.21.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_5m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

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July 14, 2023

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Certificate of analysis

Certificate No.	2023-PR-215	Receipt No.	2023-AN-185
Client	-	Date of Receipt	2023.01.18.
Client Name	-	Date of Test	2023.01.30.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_6m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) °C, Relative Humidity : (10~80) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
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July 14, 2023

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Certificate of analysis

Certificate No.	2023-PR-224	Receipt No.	2023-AN-194
Client	-	Date of Receipt	2023.04.19.
Client Name	-	Date of Test	2023.04.25.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_9m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
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July 14, 2023

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Certificate of analysis

Certificate No.	2023-PR-283	Receipt No.	2023-AN-236
Client	-	Date of Receipt	2023.07.20.
Client Name	-	Date of Test	2023.08.07.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_12m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

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August 29, 2023

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Certificate of analysis

Certificate No.	2022-PR-195	Receipt No.	2022-AN-189
Client	-	Date of Receipt	2022.08.17
Client Name	-	Date of Test	2022.08.20.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_1m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) °C, Relative Humidity : (10~80) %

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October 24, 2022

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Certificate of analysis

Certificate No.	2022-PR-204	Receipt No.	2022-AN-198
Client	-	Date of Receipt	2022.09.20
Client Name	-	Date of Test	2022.09.22
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_2m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

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October 24, 2022

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Certificate of analysis

Certificate No.	2022-PR-213	Receipt No.	2022-AN-207
Client	-	Date of Receipt	2022.10.12.
Client Name	-	Date of Test	2022.10.18.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_3m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

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October 24, 2022

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Certificate of analysis

Certificate No.	2023-PR-203	Receipt No.	2023-AN-173
Client	-	Date of Receipt	2022.11.14.
Client Name	-	Date of Test	2022.11.16.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_4m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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July 14, 2023

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Certificate of analysis

Certificate No.	2023-PR-212	Receipt No.	2023-AN-182
Client	-	Date of Receipt	2022.12.12.
Client Name	-	Date of Test	2022.12.21.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_5m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.
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July 14, 2023

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Certificate of analysis

Certificate No.	2023-PR-221	Receipt No.	2023-AN-191
Client	-	Date of Receipt	2023.01.18.
Client Name	-	Date of Test	2023.01.30.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_6m		
Manuf. Date	2021.10.05.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

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July 14, 2023

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C. L-tryptophan (Lot number: DWFP211007)

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Certificate of analysis

Certificate No.	2022-PR-187	Receipt No.	2022-AN-181
Client	-	Date of Receipt	2022.07.14
Client Name	-	Date of Test	2022.07.22.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_init		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) °C, Relative Humidity : (10~80) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
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October 24, 2022

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Certificate of analysis

Certificate No.	2022-PR-190	Receipt No.	2022-AN-184
Client	-	Date of Receipt	2022.08.17
Client Name	-	Date of Test	2022.08.20.
Client Tel	-	Use of Report	Reference test
Client Address	-		

Test Sample	L-tryptophan (TRP Pro)_25_1m
Manuf. Date	2021.10.07.
Lot. No	(b) (4)
Quantity (kg)	-

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
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October 24, 2022

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Certificate of analysis

Certificate No.	2022-PR-199	Receipt No.	2022-AN-193
Client	-	Date of Receipt	2022.09.20
Client Name	-	Date of Test	2022.09.22
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_2m		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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October 24, 2022

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Certificate of analysis

Certificate No.	2022-PR-208	Receipt No.	2022-AN-202
Client	-	Date of Receipt	2022.10.12.
Client Name	-	Date of Test	2022.10.18.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_3m		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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October 24, 2022

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Certificate of analysis

Certificate No.	2023-PR-198	Receipt No.	2023-AN-168
Client	-	Date of Receipt	2022.11.14.
Client Name	-	Date of Test	2022.11.16.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_4m		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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July 14, 2023

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Certificate of analysis

Certificate No.	2023-PR-207	Receipt No.	2023-AN-177
Client	-	Date of Receipt	2022.12.12.
Client Name	-	Date of Test	2022.12.21.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_5m		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
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July 14, 2023

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Certificate of analysis

Certificate No.	2023-PR-216	Receipt No.	2023-AN-186
Client	-	Date of Receipt	2023.01.18.
Client Name	-	Date of Test	2023.01.30.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_6m		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
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July 14, 2023

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Certificate of analysis

Certificate No.	2023-PR-225	Receipt No.	2023-AN-195
Client	-	Date of Receipt	2023.04.19.
Client Name	-	Date of Test	2023.04.25.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_25_9m		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) °C, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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July 14, 2023

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Certificate of analysis

Certificate No.	2023-PR-284	Receipt No.	2023-AN-237
Client	-	Date of Receipt	2023.07.20.
Client Name	-	Date of Test	2023.08.07.
Client Tel	-	Use of Report	Reference test
Client Address	-		

Test Sample	L-tryptophan (TRP Pro)_25_12m
Manuf. Date	2021.10.07.
Lot. No	(b) (4)
Quantity (kg)	-

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

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The Test Report cannot be reproduced, except in full.

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August 29, 2023

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Certificate of analysis

Certificate No.	2022-PR-196	Receipt No.	2022-AN-190
Client	-	Date of Receipt	2022.08.17
Client Name	-	Date of Test	2022.08.20
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_1m		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) °C, Relative Humidity : (10~80) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
The Test Report cannot be reproduced, except in full.

(b)(6)

October 24, 2022

CJ Research Institute of Biotechnology

CJ Research Institute of Biotechnology

55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, 16495, Korea, CJ BLOSSOM PARK
www.cj.co.kr
TEL : 031) 8099-2450 FAX : 031) 8099-2918

Certificate of analysis

Certificate No.	2022-PR-205	Receipt No.	2022-AN-199
Client	-	Date of Receipt	2022.09.20
Client Name	-	Date of Test	2022.09.22
Client Tel	-	Use of Report	Reference test
Client Address	-		

Test Sample	L-tryptophan (TRP Pro)_40_2m
Manuf. Date	2021.10.07.
Lot. No	(b) (4)
Quantity (kg)	-

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) °C, Relative Humidity : (10~80) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
* The Test Report cannot be reproduced, except in full

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October 24, 2022

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Certificate of analysis

Certificate No.	2022-PR-214	Receipt No.	2022-AN-208
Client	-	Date of Receipt	2022.10.12.
Client Name	-	Date of Test	2022.10.18.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_3m		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.
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October 24, 2022

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Certificate of analysis

Certificate No.	2023-PR-204	Receipt No.	2023-AN-174
Client	-	Date of Receipt	2022.11.14.
Client Name	-	Date of Test	2022.11.16.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_4m		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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July 14, 2023

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Certificate of analysis

Certificate No.	2023-PR-213	Receipt No.	2023-AN-183
Client	-	Date of Receipt	2022.12.12.
Client Name	-	Date of Test	2022.12.21.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_5m		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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July 14, 2023

CJ Research Institute of Biotechnology

CJ Research Institute of Biotechnology

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www.cj.co.kr
TEL : 031) 8099-2450 FAX : 031) 8099-2918

Certificate of analysis

Certificate No.	2023-PR-222	Receipt No.	2023-AN-192
Client	-	Date of Receipt	2023.01.18.
Client Name	-	Date of Test	2023.01.30.
Client Tel	-	Use of Report	Reference test
Client Address	-		
Test Sample	L-tryptophan (TRP Pro)_40_6m		
Manuf. Date	2021.10.07.		
Lot. No	(b) (4)		
Quantity (kg)	-		

Test Item(s)	Specification	Test Result	Test method used
L-tryptophan (dry basis)	Not less than 60 %	(b) (4)	HPLC
Loss on drying	Not more than 5 %		AOAC 934.01

* Information

* Temperature : (15~25) ℃, Relative Humidity : (10~80) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
The Test Report cannot be reproduced, except in full.

(b) (6)

July 14, 2023

CJ Research Institute of Biotechnology

(b) (4)

Test Report No. 3.808-4 L-tryptophan (TRP Pro)

(b) (4)

EFSA Study Identification: EFSA-2021 (b) (4)

Client:	CJ Europe GmbH Main Airport Center Unterschweinstiege 2-14 60549 Frankfurt am Main Germany
Subject matter:	Tests on stability of three batches L-tryptophan (TRP Pro) in a broiler mash feed
Test material:	Broiler feed "SoMi Thune 45" F-969 L-tryptophan (TRP Pro), batch (b) (4) F-959 L-tryptophan (TRP Pro), batch F-960 L-tryptophan (TRP Pro), batch F-961
Order date:	2 November 2021
Study notification date:	29 November 2021
Study co-notification date:	29 November 2021
Study date:	Preparation of broiler feed mixtures in week 1, 2022 at (b) (4) Analyses of the prepared samples during weeks 2 – 15, 2022 at (b) (4), (b)(6)
Contact person:	
Responsibilities of (b) (4):	

(b) (4)


(b) (4), (b)(6)

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CoAs L-tryptophan (TRP Pro)

Test Reports (b) Analytics Germany GmbH

(b) (4)

1. Responsibilities

Sponsor representative / monitor

(b)(6)
CJ Europe GmbH
Main Airport Center
Unterschweinstiege 2-14
60549 Frankfurt am Main
Germany
phone: (b)(6)
e-mail: (b)(6)@cj.net

Investigator

(b) (4), (b)(6)

(b) (4)

Referring to the order dated 2 November 2021, tests on the stability of three batches of L-tryptophan (TRP Pro) were performed in a broiler mash feed.

The feed mixtures were prepared in week 1, 2022, the analyses of the stability samples took place at (b) (4) Germany during weeks 2 – 15, 2022.

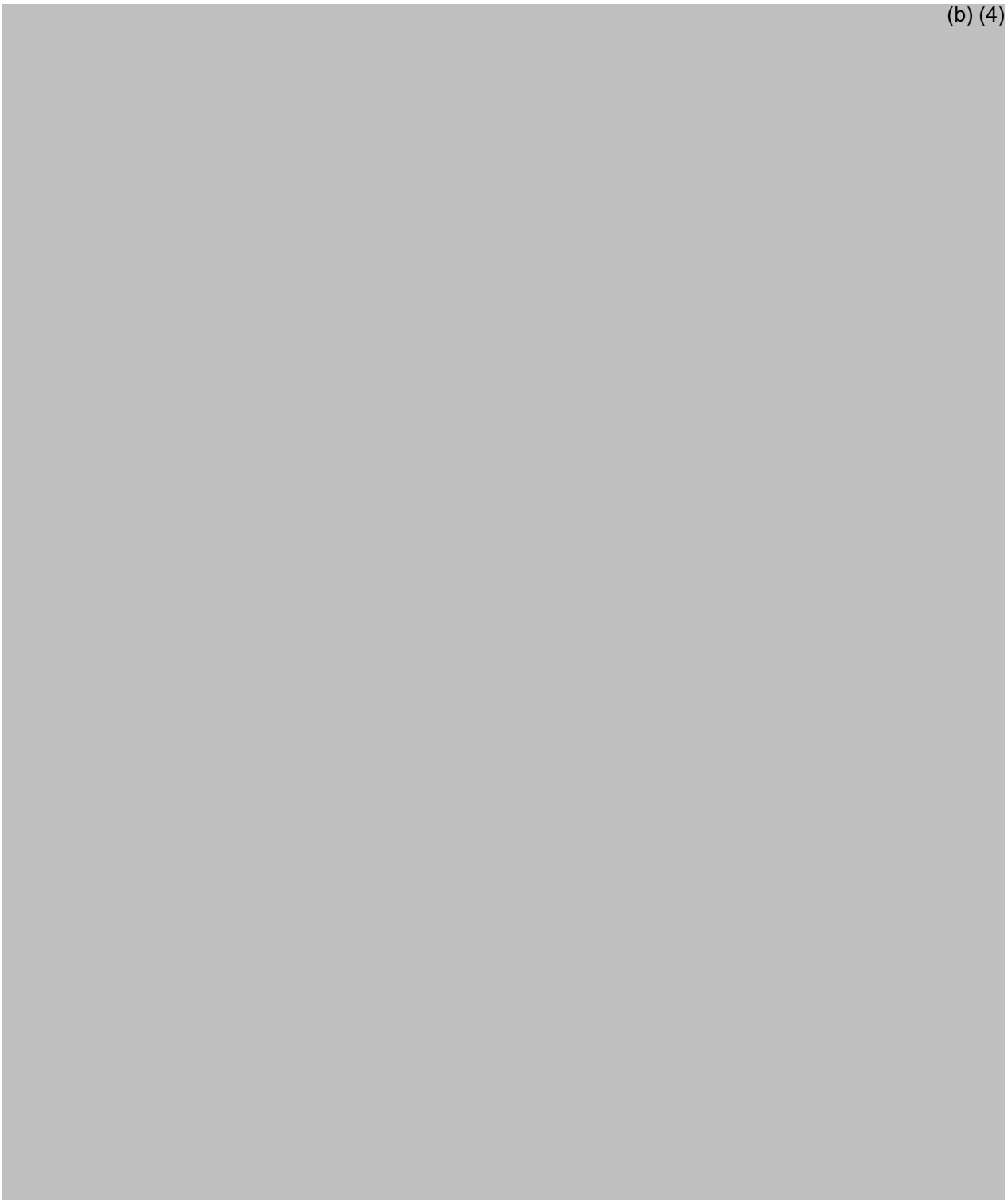
3. Test material

Broiler feed "SoMi Thune 45"		F-969
L-tryptophan (TRP Pro), batch	(b) (4)	F-959
L-tryptophan (TRP Pro), batch		F-960
L-tryptophan (TRP Pro), batch		F-961

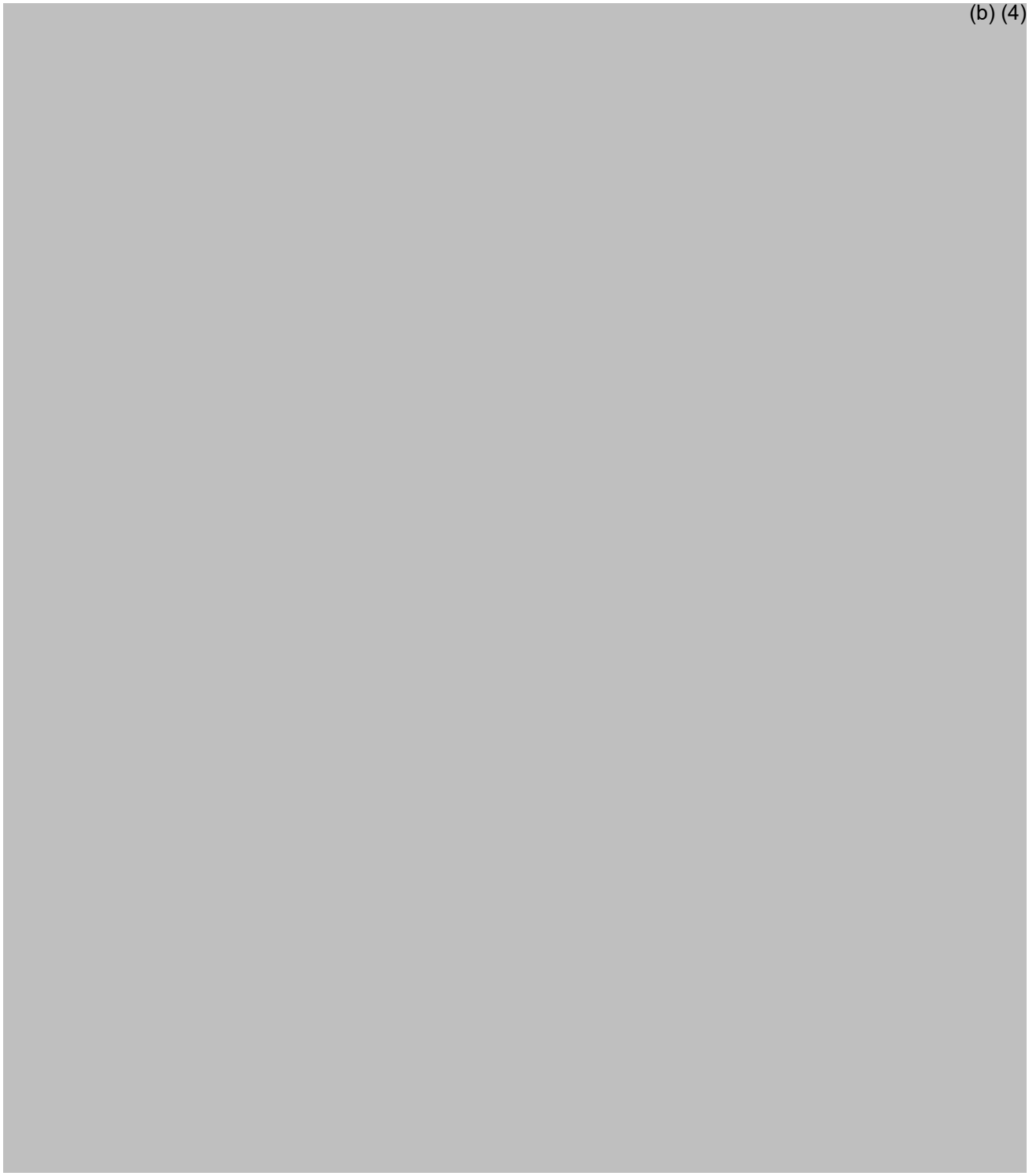
4. Material characterisation

(b) (4)


(b) (4)


(b) (4)


(b) (4)


(b) (4)

(b) (4)

8. Annex

Table 1: Formulation and ingredients of the broiler feed "SoMi Thune 45" (F-969)

Composition according to the manufacturer	**Percentage (%)**
Wheat	(b) (4)
Maize	
Soy extraction meal with stock (steamer heated)[8]	
Monocalcium phosphate	
Calcium carbonate	
Soybean oil[8]	
Sodium chloride	
Analytical components according to the manufacturer	
Crude protein	
Crude fat	
Crude fibre	
Crude ash	
Calcium	
Phosphorous	
Sodium	
Methionine	
Lysine	
Metabolisable energy	(b) (4)

Table 2: Physical material properties of the broiler feed "SoMi Thune 45" (F-969)

Physical properties	**Dimension**	**Broiler feed (F-969)**
Bulk density ρ_s	g/cm³	(b) (4)
Moisture u	%	
Particle size d_{10}	µm	
Particle size d_{50}	µm	
Particle size d_{90}	µm	
Selectivity	κ	

[8] Made from genetic modified soybeans

(b) (4)

Table 3: Composition of the premixtures for dosing the L-tryptophan (TRP Pro) into the main batches of the broiler feed

Batch description	**Ingredient**	**Amount**
Premixture with L-tryptophan (TRP Pro) F-959	Broiler feed (F-969)	(b) (4)
	L-tryptophan (TRP Pro) batch (b) (4) (F-959)	
Total batch size		
Premixture with L-tryptophan (TRP Pro) F-960	Broiler feed (F-969)	
	L-tryptophan (TRP Pro) batch (b) (4) (F-960)	
Total batch size		
Premixture with L-tryptophan (TRP Pro) F-961	Broiler feed (F-969)	
	L-tryptophan (TRP Pro) batch (b) (4) (F-961)	
Total batch size		

Table 4: Composition of the broiler feed-amino acid mixtures (main batches)

Batch No.	**Ingredient**	**Amount**
Broiler feed with L-tryptophan (TRP Pro) F-959	Broiler feed (F-969)	(b) (4)
	Premixture with L-tryptophan (TRP Pro) F-959	
Total batch size		
Broiler feed with L-tryptophan (TRP Pro) F-960	Broiler feed (F-969)	
	Premixture with L-tryptophan (TRP Pro) F-960	
Total batch size		
Broiler feed with L-tryptophan (TRP Pro) F-961	Broiler feed (F-969)	
	Premixture with L-tryptophan (TRP Pro) F-961	
Total batch size		

(b) (4)

Table 5: Sample coding broiler feed-amino acid mixtures

Batch No.	Stability samples
Broiler feed with L-tryptophan (TRP Pro) F-959	(b) (4)
Broiler feed with L-tryptophan (TRP Pro) F-960	
Broiler feed with L-tryptophan (TRP Pro) F-961	

Table 6: Analysis results of the stability samples (meal feed)[9]

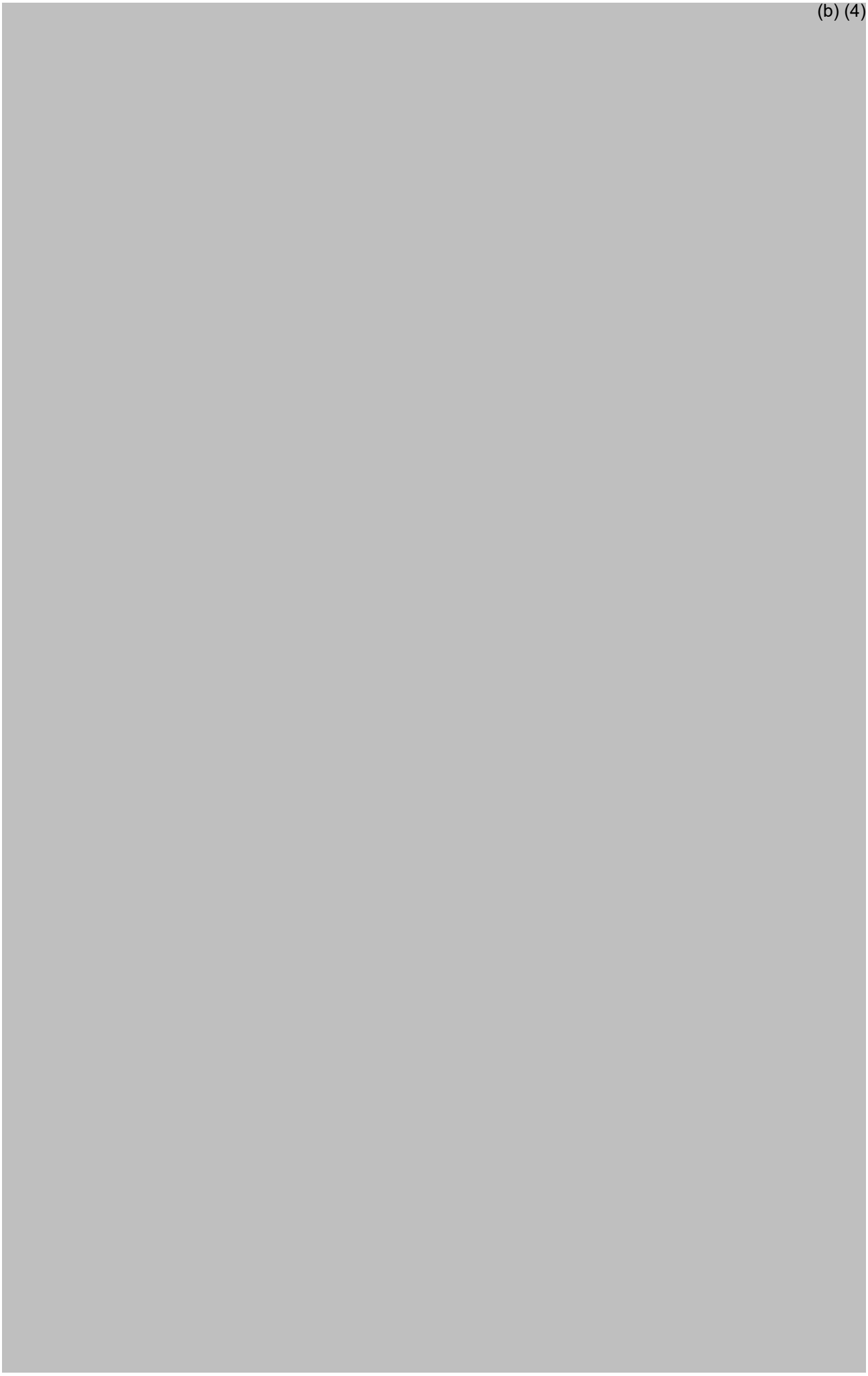
Added value 0.83 %		**Time in months**				**Mean value, SD (%)**
Mean added content: 0.508 %		**Zero**	**1**	**2**	**3**	
Mean nominal value: 0.534 %						
Sample number	**Unit**	**0 month**	**1 month**	**2 months**	**3 months**	
Analysis method	(b) (4)					
Feed blank value						
Broiler feed with L-tryptophan (TRP Pro) F-959 analysis value						0.553 ± 0.036 RSD[12] = 6.50 %
Broiler feed with L-tryptophan (TRP Pro) F-960 analysis value						0.548 ± 0.019 RSD = 3.50 %
Broiler feed with L-tryptophan (TRP Pro) F-961 analysis value						0.553 ± 0.020 RSD = 3.53 %
Mean value + standard deviation						-
Relative standard deviation (RSD)						-
Mean recovery rate						-

[9] All given values refer to the content of free amino acid.

(b) (4)

[12] RSD = relative standard deviation

(b) (4)





Stability meal feed



(b) (4)

CoAs L-tryptophan (TRP Pro)

Test Reports (b) (4) **Analytics Germany GmbH**

No. (b) (4)

No.

No.

No.

CJ Research Institute of Biotechnology

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TEL : 031) 8099-2450 FAX : 031) 8099-2918

Certificate of analysis

Certificate No.	2021-PR-212	Receipt No.	2021-AN-177
Client		Date of Receipt	2021-10-27
Client Name		Date of Test	2021-10-28
Client Tel		Use of Report	Reference test
Client Address			

Test Sample	Tryptophan (TRP Pro)
Manuf. Date	2021.09.30
Lot. No	(b) (4)
Quantity (kg)	-

Test Item(s)	Test Result	Test method used
L-Tryptophan (dry basis)	(b) (4)	HPLC
Loss on drying		AOAC 934.01

* Information

* Temperature : (20~28) ℃, Relative Humidity : (30~60) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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November 3, 2021

CJ Research Institute of Biotechnology

CJ Research Institute of Biotechnology

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TEL : 031) 8099-2450 FAX : 031) 8099-2918

Certificate of analysis

Certificate No.	2021-PR-213	Receipt No.	2021-AN-178
Client		Date of Receipt	2021-10-27
Client Name		Date of Test	2021-10-28
Client Tel		Use of Report	Reference test
Client Address			

Test Sample	Tryptophan (TRP Pro)
Manuf. Date	2021.10.05
Lot. No	(b) (4)
Quantity (kg)	-

Test Item(s)	Test Result	Test method used
L-Tryptophan (dry basis)	(b) (4)	HPLC
Loss on drying		AOAC 934.01

* Information

* Temperature : (20~28) ℃, Relative Humidity : (30~60) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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November 3, 2021

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Certificate of analysis

Certificate No.	2021-PR-214	Receipt No.	2021-AN-179
Client		Date of Receipt	2021-10-27
Client Name		Date of Test	2021-10-28
Client Tel		Use of Report	Reference test
Client Address			

Test Sample	Tryptophan (TRP Pro)
Manuf. Date	2021.10.07
Lot. No	(b) (4)
Quantity (kg)	-

Test Item(s)	Test Result	Test method used
L-Tryptophan (dry basis)	(b) (4)	HPLC
Loss on drying		AOAC 934.01

* Information

* Temperature : (20~28) ℃, Relative Humidity : (30~60) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

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November 3, 2021

CJ Research Institute of Biotechnology

(b) (4)

CJ Europe GmbH
Unterschweinstiege 2-14
60549 Frankfurt am Main
Deutschland

(b)(6)

(b) (4)

Test report for order no. (b) (4)

document no. F2022-000384-1

customer:	CJ Europe GmbH Unterschweinstiege 2-14, 60549 Frankfurt am Main
no. of samples:	27 samples
sample type:	compound feed (27x)
sampling:	customer
date of sample receipt:	07-01-2022
test period:	07-01-2022 to 03-02-2022

remark: Measurement uncertainties of the methods used can be viewed at (b) (4) The test results relate only to the items tested. This report shall not be reproduced, except in full, without written consent of (b) (4). This test report has been validated and cleared by the person mentioned below. All tests were conducted at the (b) (4) site in (b)(6) unless stated otherwise.
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(b)(6), 04-04-2022

(b) (6)

(b) (4)

(b) (6)

Test report for order no. (b) (4)

document no. (b) (4)

Product:	compound feed
sampling:	customer‡
sample transport:	courier
sample container:	plastic packaging
sample state:	flawless
date of sample receipt:	07-01-2022
flour feed:	Addition: 0,83%‡

		measurement results
	Analytical method	free tryptophan
	unit	Food-SOP 800:2020-07
sample identification	**lab no.**	% OS
labelling of sample(s): (b) (4)	L1	(b) (4)
labelling of sample(s):	L2	
labelling of sample(s):	L3	
labelling of sample(s):	L4	
labelling of sample(s):	L5	
labelling of sample(s):	L6	
labelling of sample(s):	L7	
labelling of sample(s):	L8	
labelling of sample(s):	L9	
labelling of sample(s):	L10	
labelling of sample(s):	L11	
labelling of sample(s):	L12	
labelling of sample(s):	L13	
labelling of sample(s):	L14	
labelling of sample(s):	L15	
labelling of sample(s):	L16	
labelling of sample(s):	L17	
labelling of sample(s):	L18	
labelling of sample(s):	L19	
labelling of sample(s):	L20	
labelling of sample(s):	L21	
labelling of sample(s):	L22	
labelling of sample(s):	L23	
labelling of sample(s):	L24	
labelling of sample(s):	L25	
labelling of sample(s):	L26	
labelling of sample(s):	L27	

(b) (4)

(b)(6)

(b) (4)

CJ Europe GmbH
Unterschweinstiege 2-14
60549 Frankfurt am Main
Deutschland

(b)(6)

(b) (4)

Test report for order no. (b) (4)

document no. (b) (4)

customer:	CJ Europe GmbH Unterschweinstiege 2-14, 60549 Frankfurt am Main
no. of samples:	9 samples
sample type:	compound feed (9x)
sampling:	customer
date of sample receipt:	07-02-2022
test period:	07-02-2022 to 08-03-2022

remark: Measurement uncertainties of the methods used can be viewed (b) (4) The test results relate only to the items tested. This report shall not be reproduced, except in full, without written consent of (b) (4). This test report has been validated and cleared by the person mentioned below. All tests were conducted at the (b) (4) site in (b)(6) unless stated otherwise.
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abbreviations, symbols: --: not determined, not applicable, (S) subcontraction to an accredited laboratory, (b) (4) conducted at different (b) (4) site; (N) non-accredited test method, loq: limit of quantification, n.determ.: not determined, n.a.: not applicable, n.d.: not detected, n.av.: not available, DM: dry mass, DS: dry substance, FS: fresh substance, OS: original substance, SF: surface, ‡: information provided by the customer

(b)(6)

(b)(6) 04-04-2022

(b) (4)

Product:	compound feed
sampling:	customer‡
sample transport:	courier
sample container:	plastic bag
sample state:	flawless
date of sample receipt:	07-02-2022
purchase order no.:	A.3.808‡

		measurement results
		free tryptophan
	analytical method	Food-SOP 800:2020-07
	unit	% OS
sample identification	**lab no.**	
labelling of sample(s): (b) (4) description:	L1	(b) (4)
labelling of sample(s): description:	L2	
labelling of sample(s): description:	L3	
labelling of sample(s): description:	L4	
labelling of sample(s): description:	L5	
labelling of sample(s): description:	L6	
labelling of sample(s): description:	L7	
labelling of sample(s): description:	L8	
labelling of sample(s): description:	L9	

CJ Europe GmbH
Unterschweinstiege 2-14
60549 Frankfurt am Main
Deutschland

Your contact:

Test report for order no.

document no.

customer:	CJ Europe GmbH Unterschweinstiege 2-14, 60549 Frankfurt am Main
no. of samples:	9 samples
sample type:	compound feed (9x)
sampling:	customer
date of sample receipt:	04-03-2022
test period:	04-03-2022 to 04-04-2022

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abbreviations, symbols: --: not determined, not applicable, (S) subcontraction to an accredited laboratory, conducted at different site; (N) non-accredited test method, loq: limit of quantification, n.determ.: not determined, n.a.: not applicable, n.d.: not detected, n.av.: not available, DM: dry mass, DS: dry substance, FS: fresh substance, OS: original substance, SF: surface, ‡: information provided by the customer

04-04-2022

(b) (4)

(b)(6)

Test report for order no. (b) (4)
document no. (b) (4)

product:	compound feed
sampling:	customer‡
sample transport:	courier
sample container:	plastic packaging
sample state:	flawless
date of sample receipt:	04-03-2022
purchase order no.:	A.3.808‡

		measurement results
		free tryptophan
	analytical method	Food-SOP 800:2020-07
	unit	% OS
sample identification	**lab no.**	
labelling of sample(s): (b) (4) description: Addition:	L1	(b) (4)
labelling of sample(s): description: Addition:	L2	
labelling of sample(s): description: Addition:	L3	
labelling of sample(s): description: Addition:	L4	
labelling of sample(s): description: Addition:	L5	
labelling of sample(s): description: Addition:	L6	
labelling of sample(s): description: Addition:	L7	
labelling of sample(s): description: Addition:	L8	
labelling of sample(s): description: Addition:	L9	

(b) (4)

(b) (4), (b)(6)

(b) (4)

CJ Europe GmbH
Unterschweinstiege 2-14
60549 Frankfurt am Main

(b)(6)

Test report for order no. (b) (4)
document no. (b) (4)

(b) (4)

customer:	CJ Europe GmbH Unterschweinstiege 2-14, 60549 Frankfurt am Main
no. of samples:	9 samples
sample type:	compound feed (9x)
sampling:	customer
date of sample receipt:	04-04-2022
test period:	04-04-2022 to 14-04-2022

remark: Measurement uncertainties of the methods used can be viewed at (b) (4). The test results relate only to the items tested. This report shall not be reproduced, except in full, without written consent of (b) (4). This test report has been validated and cleared by the person mentioned below. All tests were conducted at the (b) site in (b)(6) unless stated otherwise.

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abbreviations, symbols: --: not determined, not applicable, (S) subcontraction to an accredited laboratory, (b) (4) conducted at different (b) (4) site; (N) non-accredited test method, loq: limit of quantification, n.determ.: not determined, n.a.: not applicable, n.d.: not detected, n.av.: not available, DM: dry mass, DS: dry substance, FS: fresh substance, OS: original substance, SF: surface, ‡: information provided by the customer

(b)(6)

(b)(6) 14-04-2022

(b) (4)

(b) (4)

Produkt:	compound feed
sampling:	customer‡
sample transport:	courier
sample container:	plastic packaging
sample state:	flawless
date of sample receipt:	04-04-2022
purchase order no.:	A.3.808‡

			measurement results
			free tryptophan
		analytical method	Food-SOP 800:2020-07
		unit	% OS
sample identification		**lab no.**	
labelling of sample(s):	(b) (4)	L1	(b) (4)
description:			
Addition:			
labelling of sample(s):		L2	
description:			
Addition:			
labelling of sample(s):		L3	
description:			
Addition:			
labelling of sample(s):		L4	
description:			
Addition:			
labelling of sample(s):		L5	
description:			
Addition:			
labelling of sample(s):		L6	
description:			
Addition:			
labelling of sample(s):		L7	
description:			
Addition:			
labelling of sample(s):		L8	
description:			
Addition:			
labelling of sample(s):		L9	
description:			
Addition:			

[redacted] (b) (4)

Test Report No. 3.808-1 L-tryptophan (TRP Pro)

[redacted] (b) (4)

EFSA Study Identification: EFSA-2021-00006573

Client:	CJ Europe GmbH Main Airport Center Unterschweinstiege 2-14 60549 Frankfurt am Main Germany
Subject matter:	Tests on homogeneity of one batch L-tryptophan (TRP Pro) in a broiler mash feed
Test material:	Broiler feed "SoMi Thune 45" F-969 L-tryptophan (TRP Pro), batch [redacted] (b) (4) F-959
Order date:	2 November 2021
Study notification date:	29 November 2021
Study co-notification date:	29 November 2021
Study date:	Preparation of a broiler feed mixture in week 1, 2022 at [redacted] (b) Analyses of the prepared samples during weeks 2 – 5, 2022 at [redacted] (b) (4), (b) (6)
Contact person:	[redacted] (b)(6)
Responsibilities of [redacted]	[redacted] (b) (6)

[redacted] (b) (4)


(b) (4), (b)(6)

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CoA L-tryptophan (TRP Pro)

Test Report (b) (4)

1. Responsibilities

Sponsor representative / monitor

(b)(6)
CJ Europe GmbH
Main Airport Center
Unterschweinstiege 2-14
60549 Frankfurt am Main
Germany
phone: (b)(6)
e-mail:

Investigator

(b) (4), (b)(6)

2. Objective

(b) (4)

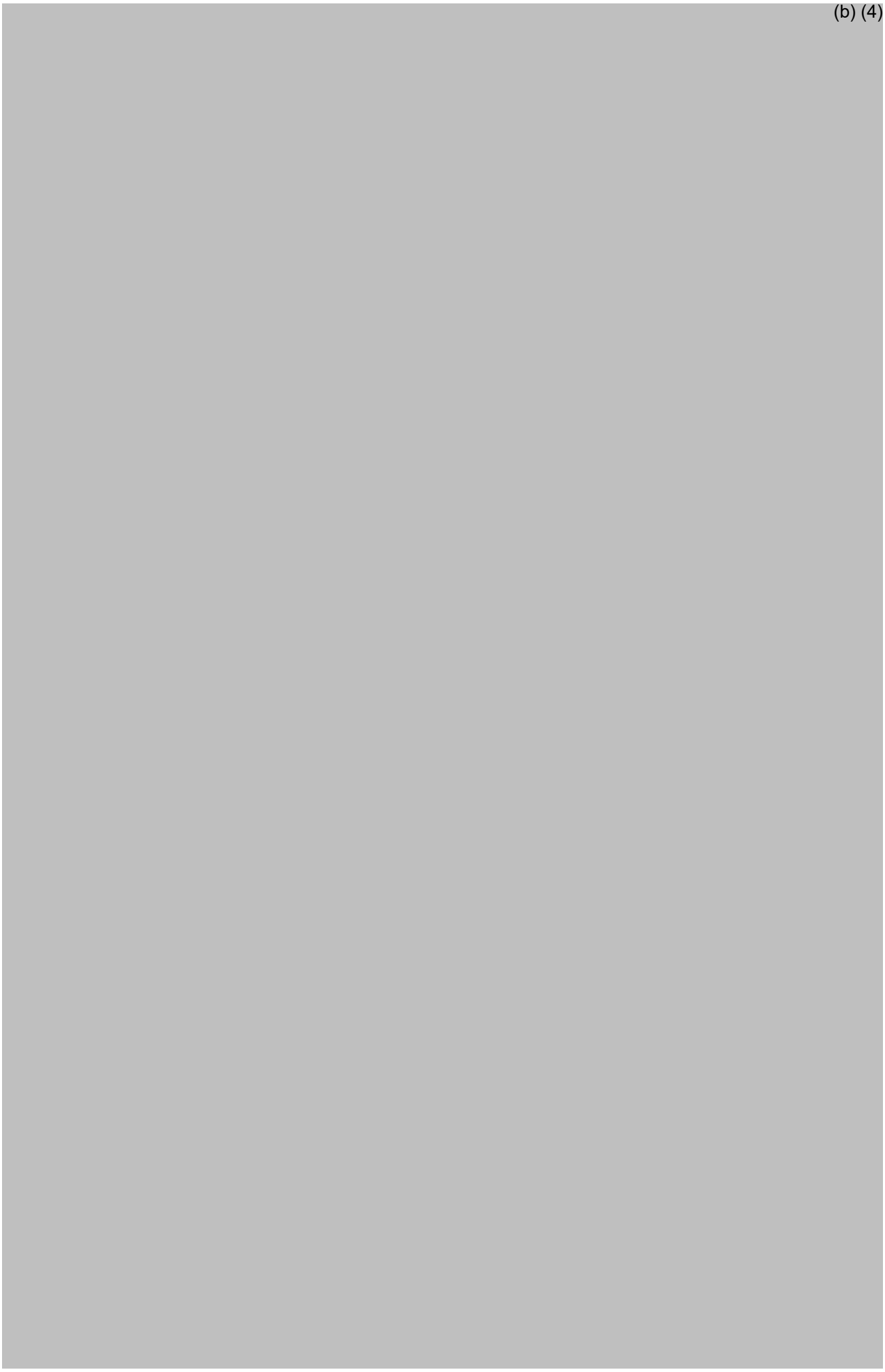
(b) (4)

(b) (4)

[redacted]



(b) (4)


(b) (4)

(b) (4)

Table 3: Composition of the premixture for dosing the L-tryptophan (TRP Pro) into the main batch

(b) (4)

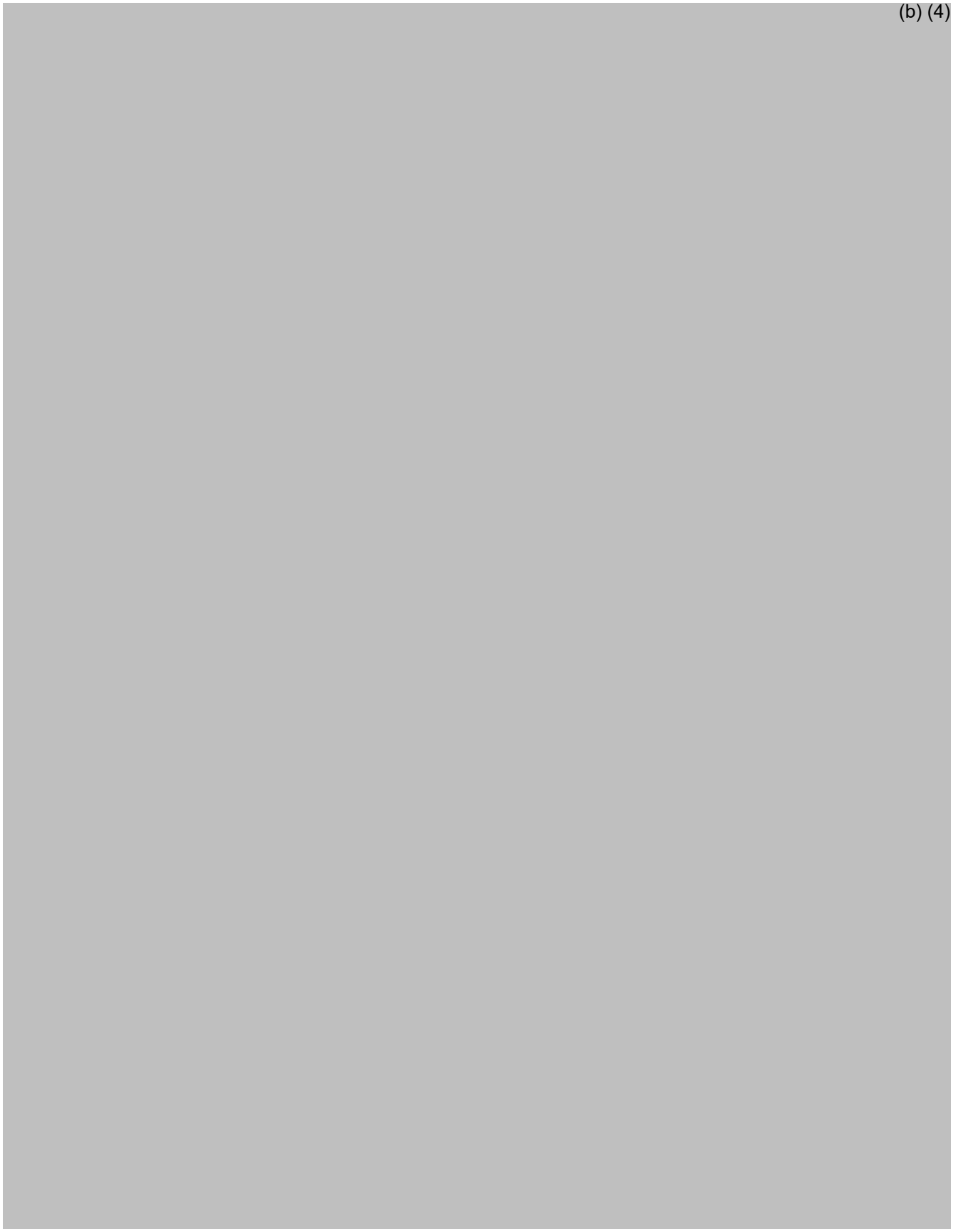
(b) (4)



(b) (4)



(b) (4)



(b) (4)

Appendices

CoA L-tryptophan (TRP Pro)

Test Report (b) (4)

CJ Research Institute of Biotechnology

55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, 16495, Korea, CJ BLOSSOM PARK

www.cj.co.kr

TEL : 031) 8099-2450 FAX : 031) 8099-2918

Certificate of analysis

Certificate No.	2021-PR-212	Receipt No.	2021-AN-177
Client		Date of Receipt	2021-10-27
Client Name		Date of Test	2021-10-28
Client Tel		Use of Report	Reference test
Client Address			

Test Sample	L-tryptophan (TRP Pro)
Manuf. Date	2021.09.30
Lot. No	(b) (4)
Quantity (kg)	-

Test Item(s)	Test Result	Test method used
L-Tryptophan (dry basis)	(b) (4)	HPLC
Loss on drying		AOAC 934.01

* Information

* Temperature : (20~28) ℃, Relative Humidity : (30~60) %

* The results shown in this test report refer only to the sample tested unless otherwise stated.

The Test Report cannot be reproduced, except in full.

(b)(6)

November 3, 2021

CJ Research Institute of Biotechnology

(b) (4)

CJ Europe GmbH
Unterschweinstiege 2-14
60549 Frankfurt am Main
Deutschland

(b) (4), (b) (6)

(b) (4)

Test report for order no. (b) (4)

document no. (b) (4)

customer:	CJ Europe GmbH Unterschweinstiege 2-14, 60549 Frankfurt am Main
no. of samples:	27 samples
sample type:	compound feed (27x)
sampling:	customer
date of sample receipt:	07-01-2022
test period:	07-01-2022 to 03-02-2022

remark: Measurement uncertainties of the methods used can be viewed at: (b) (4)

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abbreviations, symbols: --: not determined, not applicable, (S) subcontraction to an accredited laboratory, (b) (4) conducted at different SGS site; (N) non-accredited test method, loq: limit of quantification, n.determ.: not determined, n.a.: not applicable, n.d.: not detected, n.av.: not available, DM: dry mass, DS: dry substance, FS: fresh substance, OS: original substance, SF: surface, ‡: information provided by the customer

(b)(6)

(b) (4) 04-04-2022

Test report for order no. (b) (4)

document no. (b) (4)

Product:	compound feed
sampling:	customer‡
sample transport:	courier
sample container:	plastic packaging
sample state:	flawless
date of sample receipt:	07-01-2022
flour feed:	Addition: 0,83%‡

		measurement results
		free tryptophan
	Analytical method	Food-SOP 800:2020-07
	unit	% OS
sample identification	**lab no.**	

(b) (4)

(b) (4)

CJ Europe GmbH
Unterschweinstiege 2-14
60549 Frankfurt am Main

Test Report 5898962
Order No. 6253079
Customer No. 10114507

(b) (6)

(b) (4)

Hamburg, 22.07.2022

Your order/project: .
Your purchase order date: 29.06.2022

(b) (4)

(b) (4),
(b)(6)

(b) (4)

General Information:

Sample No.:	220749233
Sample:	L-tryptophan (TRP Pro) Corynebacterium glutamicum KCCM 80346 Batch No.: (b) (4)
Date of receipt:	07.07.2022
Testing period (begin / end):	08.07.2022 / 12.07.2022
Quantity:	219g
Packaging:	Aluminium bag

Test Results:

Parameter	Method	Lab	Unit	Result	Limit of quantification	Requirements
Minerals/metals:						
Lead	DIN EN 15763, mod.	HH	mg/kg	0,028	0,015	
Cadmium	DIN EN 15763, mod.	HH	mg/kg	< 0,010	0,010	
Mercury	DIN EN 15763, mod.	HH	mg/kg	< 0,010	0,010	
Arsenic	DIN EN 15763, mod.	HH	mg/kg	0,15	0,04	

(b) (4)

(b) (4)

General Information:

Sample No.:	220749234
Sample:	L-tryptophan (TRP Pro) Corynebacterium glutamicum KCCM 80346 Batch No.: (b) (4)
Date of receipt:	07.07.2022
Testing period (begin / end):	08.07.2022 / 12.07.2022
Quantity:	231g
Packaging:	Aluminium bag

Test Results:

Parameter	Method	Lab	Unit	Result	Limit of quantification	Requirements
Minerals/metals:						
Lead	DIN EN 15763, mod.	HH	mg/kg	0,025	0,015	
Cadmium	DIN EN 15763, mod.	HH	mg/kg	< 0,010	0,010	
Mercury	DIN EN 15763, mod.	HH	mg/kg	< 0,010	0,010	
Arsenic	DIN EN 15763, mod.	HH	mg/kg	0,15	0,04	

(b) (4)

(b) (4)

General Information:

Sample No.:	220749235
Sample:	L-tryptophan (TRP Pro) Corynebacterium glutamicum KCCM 80346 Batch No.: (b) (4)
Date of receipt:	07.07.2022
Testing period (begin / end):	08.07.2022 / 12.07.2022
Quantity:	223g
Packaging:	Aluminium bag

Test Results:

Parameter	Method	Lab	Unit	Result	Limit of quantification	Requirements
Minerals/metals:						
Lead	DIN EN 15763, mod.	HH	mg/kg	0,023	0,015	
Cadmium	DIN EN 15763, mod.	HH	mg/kg	< 0,010	0,010	
Mercury	DIN EN 15763, mod.	HH	mg/kg	< 0,010	0,010	
Arsenic	DIN EN 15763, mod.	HH	mg/kg	0,14	0,04	

Summary of used test methods:

DIN EN 15763, mod.	2010-04, Modification: additional Elements for IntStd (In, Sc). Additional elements are measured. extended measurement uncertainty (relative) with p = 95 %, k = 2 (sampling was not taken into account): 46 %, for Aluminium, determined on food and feed with < 1 mg/kg 16 %, for Aluminium, determined on food and feed with 1-10 mg/kg 8 %, for Aluminium, determined on food and feed with > 10 mg/kg 22 %, for Arsenic, determined on food and feed with < 0,08 mg/kg 16 %, for Arsenic, determined on food and feed with 0,08-15 mg/kg 11 %, for Barium, determined on food and feed with < 1 mg/kg 7 %, for Barium, determined on food and feed with 1-5 mg/kg 4 %, for Barium, determined on food and feed with > 5 mg/kg 24 %, for Cadmium, determined on food and feed with < 1,1 mg/kg 55 %, for Chromium, determined on food and feed with < 1 mg/kg 20 %, for Chromium, determined on food and feed with > 1 mg/kg 11 %, for Cobalt, determined on food and feed with < 0,1 mg/kg 8 %, for Cobalt, determined on food and feed with 0,1-1 mg/kg 17 %, for Copper, determined on food and feed with < 16 mg/kg 5 %, for Copper, determined on food and feed with > 16 mg/kg 58 %, for Iron, determined on food and feed with < 0,2 mg/kg 14 %, for Iron, determined on food and feed with 0,2-16,2 mg/kg 7 %, for Iron, determined on food and feed with > 16,2 mg/kg 24 %, for Lead, determined on food and feed with < 1,5 mg/kg 59 %, for Lithium, determined on food and feed with < 0,2 mg/kg 47 %, for Lithium, determined on food and feed with > 0,2 mg/kg 18 %, for Manganese, determined on food and feed with < 1 mg/kg 7 %, for Manganese, determined on food and feed with 1-10 mg/kg 5 %, for Manganese, determined on food and feed with > 10 mg/kg 25 %, for Mercury, determined on food and feed with < 0,25 mg/kg

(b) (4)

(b) (4)

	12 %, for Molybdenum, determined on food and feed with < 1 mg/kg 11 %, for Molybdenum, determined on food and feed with 1-10 mg/kg 6 %, for Molybdenum, determined on food and feed with > 10 mg/kg 21 %, for Nickel, determined on food and feed with < 0,1 mg/kg 8 %, for Nickel, determined on food and feed with 0,1-0,5 mg/kg 5 %, for Nickel, determined on food and feed with > 0,5 mg/kg 19 %, for Selenium, determined on food and feed with < 0,1 mg/kg 5 %, for Selenium, determined on food and feed with > 0,1 mg/kg 6 %, for Silver, determined on sheimp meal with 0,58 mg/kg 8 %, for Thallium, determined on chocolate with 0,01 mg/kg 10 %, for Vanadium, determined on food and feed with < 0,3 mg/kg 4 %, for Vanadium, determined on food and feed with > 0,3 mg/kg 20 %, for Zinc, determined on food and feed with < 4 mg/kg 16 %, for Zinc, determined on food and feed with 4-72 mg/kg The sample-specific measurement uncertainty was not determined and can deviate.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Final Report

Test Facility Study No. (b) (4)

Sponsor Reference No. (b) (4)

90-Day Repeated Dose Toxicity Study of L-Tryptophan (TRP Pro) by the Oral (Gavage) Route in the Wistar Han IGS Rat with a 4-Week Recovery Period

GLP

SPONSOR:
CJ CheilJedang Corporation
55-42 Beongil Gwanggyo-ro, Yeongtong-gu
Suwon-si
16495 Gyeonggi-do
Republic of Korea

(b) (4)

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Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

(b) (4) **STATEMENT**

Study Number: (b) (4)

This study has been audited by (b) (4) in accordance with the applicable Good Laboratory Practice regulations. Reports were submitted in accordance with Standard Operating Procedures as follows:

(b) (4) INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Dates Findings Submitted to: Study Director Management
05Oct2022	Final Study Plan	06Oct2022	06Oct2022
19Oct2022	Study Plan Amendment 01	19Oct2022	19Oct2022
16Nov2022	Study Plan Amendment 02	16Nov2022	16Nov2022
09Dec2022	Study Plan Amendment 03	09Dec2022	09Dec2022
06Feb2023	Study Plan Amendment 04	07Feb2023	07Feb2023
17Oct2022	Dose Preparation	17Oct2022	17Oct2022
22Nov2022	Arena Observations	22Nov2022	22Nov2022
16Jan2023	Sperm Analysis	16Jan2023	16Jan2023
24Jan2023	Urinalysis Osmolality	24Jan2023	24Jan2023
14Feb2023	Blood Sampling	14Feb2023	14Feb2023
25Jul2022	Dispensary: Sample dispatch*	27Jul2022	27Jul2022
31Oct2022	Dose administration*	31Oct2022	31Oct2022
28Feb2022	Ophthalmological examination*	02Mar2022	02Mar2022
25Jan2022	Body weighing*	25Jan2022	25Jan2022
01Feb2023	In life mesurements*	02Feb2023	02Feb2023
14Nov2022	Blood sampling*	15Nov2022	15Nov2022
07Feb2023	Clinical Observations*	07Feb2023	07Feb2023
07Feb2023-08Feb2023	Neurobehavioural Tests*	08Feb2023	08Feb2023
07Feb2023	Functional Observation Battery *	07Feb2023	07Feb2023
22Aug2023	Vaginal Smear*	22Aug2023	22Aug2023
13Jan2023-16Jan2023	Blood sample processing*	16Jan2023	16Jan2023
26Jan2023	Clinical pathology: Sample reception, preparation, analysis and storage*	26Jan2023	26Jan2023
14Feb2023	Sample Dispatch*	14Feb2023	14Feb2023
15Feb2023	Necropsy*	15Feb2023	15Feb2023
21Mar2023-04Apr2023	Histology process*	04Apr2023	04Apr2023
23Mar2023	Clinical pathology Slides management*	23Mar2023	23Mar2023
03May2023-05May2023	Pathology Slide Management*	05May2023	05May2023

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
21Mar2023-31Mar2023	Data Integrity of study records; study plan and amendments, final report, contributing reports, deviations, study notes*	31Mar2023	31Mar2023
14Feb2023-15Feb2023 15Mar2023-30Mar2023	Archiving process*	15Feb2023 30Mar2023	15Feb2023 30Mar2023
06Apr2023	Report - Pathology	07Apr2023	07Apr2023
06Apr2023-07Apr2023	Data Review - Necropsy	07Apr2023	07Apr2023
19Apr2023-26Apr2023	Report - Materials and Methods	26Apr2023	26Apr2023
19Apr2023-26Apr2023	Report Tables	26Apr2023	26Apr2023
19Apr2023-26Apr2023	Data Review - Technical Operations	26Apr2023	26Apr2023
19Apr2023-26Apr2023	Data Review - Clinical Pathology	26Apr2023	26Apr2023
19Apr2023-26Apr2023	Report	26Apr2023	26Apr2023
19Apr2023-26Apr2023	Report - Ophthalmology	26Apr2023	26Apr2023
19Apr2023-26Apr2023	Report – Neuropathology (FOB)	26Apr2023	26Apr2023
19Apr2023-26Apr2023	Data Review - Necropsy	26Apr2023	26Apr2023
24Apr2023-25Apr2023	Data Review - Formulations	26Apr2023	26Apr2023
31Aug2023-04Sep2023	Report - Results	04Sep2023	04Sep2023
09Oct2023-10Oct2023	Report - Results	10Oct2023	10Oct2023

*Process-based inspections relevant to this study were conducted according to a predetermined schedule.

In addition to the above-mentioned audits, routine facility inspections were also conducted during the course of this study. Inspection findings, if any, specific to this study were reported by (b) (4) to the Study Director and Management and listed as a Phase Audit on this (b) (4) Statement.

The (b) (4) Statements for the work conducted at the Test Sites were reviewed and are included in the appropriate section of this report.

The Final Report has been reviewed to assure that it accurately describes the materials and methods, and that the reported results accurately reflect the raw data.

All electronic signatures appear at the end of the document.

GLP COMPLIANCE STATEMENT AND REPORT APPROVAL

The study was performed in accordance with OECD Principles of Good Laboratory Practice as required in Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004, and Good Laboratory Practices in Article Annexe II de l'article D523-8 du code de l'environnement.

OECD Principles of Good Laboratory Practice are accepted by Regulatory Authorities throughout the European Union, United States of America (FDA and EPA) and Japan (MHLW, MAFF, and METI), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Formulation analysis (Appendix 3) and thyroid hormone analysis (Appendix 26) conducted in Hungary were performed in compliance with the principles of Good Laboratory Practice Regulations as specified in the Hungarian Good Laboratory Practice Regulations of 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities. Those regulations correspond to the OECD Principles of Good Laboratory Practice (OECD GLP, ENV/MC/CHEM (98) 17) and as accepted by Regulatory Authorities throughout the European Union, United States of America, Japan, and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

This study was conducted in accordance with the procedures described herein. All deviations authorized/acknowledged by the Study Director are documented in the study records. The report represents an accurate and complete record of the results obtained.

There were no deviations from the above regulations that affected the overall integrity of the study or the interpretation of the study results and conclusions.

All electronic signatures appear at the end of the document.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

1. RESPONSIBLE PERSONNEL

(b) (4), (b)(6)

2. SUMMARY

The objective of this study was to determine the potential toxicity of L-tryptophan (TRP Pro) when given by the oral (gavage) route for 90 days to the Wistar Han IGS rat and to evaluate the potential reversibility of any findings after a 4-week recovery period. The control group received purified water as the vehicle control.

The study design was as follows:

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume[a] (mL/kg)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Vehicle control	0	10	0	10	10	5	5
2	Test item	500	10	50	10	10	-	-
3	Test item	1000	10	100	10	10	-	-
4	Test item	2000	10	200	10	10	5	5

- = Not applicable.
[a] Based on the most recent body weight measurement.

The following parameters and end points were evaluated in this study: mortality, clinical signs, arena observations, body weights, body weight gains, food consumption, behavioral functional observational battery, locomotor activity test (motor monitor test), ophthalmology, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), thyroid hormone analysis, stage of estrous at necropsy, sperm analysis, organ weights, macroscopic and microscopic examinations.

The dose formulation analysis of samples collected on Day 1 and at Week 13 were within the acceptable range of the concentration and homogeneity margin.

There was no L-tryptophan (TRP Pro)-related death or change on FOB, locomotor activity, or ophthalmic examinations during the study. Clinical observations were limited to slight to severe salivations at all doses with salivation-related reflexes (pedaling and ploughing) noted at ≥ 1000 mg/kg/day with a dose-related incidence. These observations were transiently noted after dosing and were considered non-adverse.

There was a slight and non-adverse lower body weight gain in males at ≥ 1000 mg/kg/day from Day 16 to Day 36 that did not impact the body weight over the dosing period. A slight and non-adverse decrease in male body weights at 1000 mg/kg/day was noted on Day 90. There was a slightly lower food consumption in males given 1000 mg/kg/day over the dosing period while the food intake was slightly higher in treated females at ≥ 1000 mg/kg/day.

Clinical pathology parameter changes were limited to changes in PT for males at 2000 mg/kg/day and APTT for females ≥ 1000 mg/kg/day. These changes were of low magnitude, not observed at the end of the recovery period, and were therefore not considered adverse. Urinalysis showed a non-adverse lower urine pH for treated animals at the end of the dosing period, that was not noted thereafter.

There was no consistent trend amongst the treated groups for either sex to suggest any effect of the treatment on T3, T4, or TSH hormone analysis at 500, 1000, or 2000 mg/kg/day at the end of the dosing, or the recovery period.

Administration of L-tryptophan (TRP Pro) did not result at terminal euthanasia or recovery period in any premature mortality, gross lesions or organ weight changes. In addition, there was no evidence of treatment-related microscopic findings in the tissues examined at 2000 mg/kg/day. Histopathological findings were considered incidental or part of the normal background and unrelated to administration of L-tryptophan (TRP Pro). In the absence of target tissues at microscopic evaluation of main study animals, the histological evaluation of organs/tissues in animals from the 4-week recovery euthanasia (Day 120) was not required.

In addition, there was no change in the sperm count, sperm motility, and sperm morphology in treated males, at any dose level.

In conclusion, administration of L-tryptophan (TRP Pro) by once daily oral gavage was well tolerated in rats at levels up to 2000 mg/kg/day. Clinical observations were limited to non-adverse salivations with associated pedaling and ploughing reflexes noted at ≥ 1000 mg/kg/day. There were non-adverse changes noted on body weights and food consumption at ≥ 1000 mg/kg/day as well as non-adverse coagulation parameter and urine pH changes at ≥ 1000 mg/kg/day. There were no gross lesions, organ weight changes, and evidence of treatment-related microscopic findings at necropsy. Based on these results, the no observed adverse effect level (NOAEL) was considered to be 2000 mg/kg/day.

3. INTRODUCTION

The objective of this study was to determine the potential toxicity of L-tryptophan (TRP Pro) when given by the oral (gavage) route for 90 days to the Wistar Han IGS rat and to evaluate the potential reversibility of any findings after a 4-week recovery period.

The design of this study was based on the study objective, the overall product development strategy for the test item, and the following study design guidelines:

- OECD Guideline 408 (2018). Repeated Dose 90-day Oral Toxicity Study in Rodents
- EPA Health Effects Test Guideline OPPTS 870.3100: 90-Day Oral Toxicity in Rodents

The Study Plan, the last Study Plan amendment, and deviations are presented in Appendix 1.

Study Initiation Date:	04 Oct 2022
Initiation of Dosing:	18 Oct 2022
Completion of In-Life:	End of dosing period: 16 and 17 Jan 2023
	End of recovery period: 14 Feb 2023
Experimental Starting Date:	10 Oct 2022 (animal arrival)
Experimental Completion Date:	01 Aug 2023 (last date on which data were collected)

4. MATERIALS AND METHODS

4.1. Test Materials Identification

4.1.1. Test Item Characterization

The Sponsor provided to the Test Facility documentation of the identity, strength, purity, composition, and stability for the test item. A certificate of analysis was provided to the Test Facility and is presented in Appendix 2.

The characterization of the test item formulation was conducted by the Study Sponsor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated.

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the test item, and this information is available to the appropriate regulatory agencies should it be requested.

4.1.2. Test Materials Identification

Text Table 2
Test Item Identification

	Test Item
Identification:	L-tryptophan (TRP Pro)[a]
Alternate Identifications:	TRP Pro/Tryptophan (TRP Pro)
Batch/Lot No.:	(b) (4)
Expiration Date:	04 Oct 2023 (information given by the Sponsor, i.e., 2 years after the manufacturing date [05 Oct 2021])
Physical Description:	Light brown granule
Percentage of Active Compound:	61.34% of L-tryptophan
Correction Factor:	None
Storage Conditions:	Controlled room temperature between +15°C and +25°C, protected from light and humidity
Provided by:	Sponsor

[a] Identification and alternate identification are synonyms, therefore, in the Phase Reports and expert reports all denominations are used indifferently.

Text Table 3
Vehicle Control Identification

	Vehicle Control
Identification:	Purified water
Alternate Identification:	OTEC H_2O sterile water for technical use
Batch/Lot Nos.:	(b) (4)
Expiration Dates:	30 Nov 2023 and 31 May 2024
Storage Conditions:	Ambient or room temperature
Provided by:	Laboratoire Aguettant

4.2. Reserve Samples

For each batch (lot) of test item, a reserve sample (0.1 g) was collected and maintained under the appropriate storage conditions by the Test Facility.

4.3. Test Item Inventory and Disposition

The test item was received by the Test Facility for distribution as needed. Records of the receipt, distribution, storage, and disposition of the test item were maintained. All unused Sponsor-supplied bulk test item, with the exception of reserve samples, was discarded.

4.4. Dose Formulation and Analysis

4.4.1. Preparation of Formulations

Dose formulations were prepared on a weekly basis and divided into aliquots to be dispensed on each dosing occasion.

Text Table 4
Formulation Frequency of Preparation

Dose Formulation	Administration Dose Form	Frequency of Preparation	Storage Conditions
Vehicle control	Solution	Not applicable (commercial vehicle)	Room or ambient temperature
Test item	Suspension	Weekly	Immediately dispensed at ambient temperature

Any residual volumes from each dosing occasion were discarded.

4.4.2. Preparation Details

Dosing formulations were prepared at appropriate concentrations to meet dose level requirements according to Standard Operating Procedures of the Test Facility. Formulations were stirred with magnetic stirrer from the preparation until completion of each treatment (except during transfer to the animal facility).

4.4.3. Sample Collection and Analysis

Dose formulation samples were collected for analysis as indicated in the following table.

Text Table 5
Dose Formulation Sample Collection Schedule

Sample Type	Concentrations	Stratum	Sampling From	No. of Samples per Concentration			Sample Volume (mL/g)[b]	Intervals
				Collected	Analyzed	Backup		
Concentration analysis	Groups 1 and 3	Middle	Preparation vessel	5	2	3	1	Day 1
Concentration/ Homogeneity analysis[a]	Groups 2 and 4	Top		5	2	3	1	Day 1
		Middle		5	2	3	1	
		Bottom		5	2	3	1	
Concentration analysis	All groups	Middle		5	2	3	1	Week 13[c]
				5	2	3	1	Week 13[d]

[a] The averaged result from homogeneity analysis served as concentration verification.
[b] Sample size: 1 mL for solutions, 1 g for suspensions.
[c] Sampled right after the last preparation.
[d] Sampled 8 days after the last preparation, under constant stirring.

All samples to be analyzed were shipped in dry ice to the Test Site for analysis as described in Appendix 1.

4.4.3.1. Analytical Method

Analyses were performed using a validated HPLC-UV (high performance liquid chromatography with UV detection) analytical method (Test Site Study No. 21/300-316AN).

During the analysis, the active ingredient (L-tryptophan) was analyzed directly.

Concentrations of test formulations were quantified based on its active ingredient content.

4.4.3.2. Concentration and Homogeneity Analysis

Homogeneity was assessed for Group 2 and 4 formulations by measuring the achieved concentration in the top, middle, and bottom samples.

Methods and results are presented in Appendix 3.

4.4.3.3. Stability Analysis

Stability analyses performed previously in conjunction with Test Site Study No. 21/300-316AN demonstrated that the test item is stable in the vehicle control when prepared and stored under the same conditions at concentrations bracketing those used in the present study (see Appendix 1).

Stability data have been retained in the study records of Test Site Study No. 21/300-316AN.

4.5. Test System

4.5.1. Receipt

On 10 Oct 2022, Wistar Han IGS rats were received from (b) (4)

Animals were approximately 6 weeks old and weighed between 161 and 222 g (males) and between 134 and 176 g (females) at the initiation of dosing.

4.5.2. Justification for Test System and Number of Animals

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models which do not use live animals currently do not exist.

The rat was chosen as the animal model for this study as it is an accepted rodent species for toxicity testing by regulatory agencies.

The total number of animals used in this study was considered to be the minimum required to properly characterize the effects of the test item. This study had been designed such that it did not require an unnecessary number of animals to accomplish its objective.

4.5.3. Animal Identification

Animals were identified using a subcutaneously implanted electronic identification chip.

4.5.4. Environmental Acclimation

All animals received a clinical inspection for ill-health on arrival. Acclimation period was 8 days before the start of dosing.

4.5.5. Selection, Assignment, Replacement, and Disposition of Animals

Animals were randomly assigned to groups at receipt. The randomization resulted in comparable mean body weight values among the groups (i.e., ± 20% of the mean).

There was no animal replacement during the study.

The disposition of all animals was documented in the study records.

4.5.6. Husbandry

4.5.6.1. Housing

Animals were group housed (up to 5 animals of the same sex and same dosing group together) in plastic cages containing appropriate bedding.

Cages were identified using color-coded cage cards indicating study, group, animal numbers, and sex.

Animals were separated during designated procedures/activities or as required for monitoring and/or health purposes, as deemed appropriate by Study Director and/or Clinical Veterinarian.

Cages were arranged on the racks in group order.

4.5.6.2. Animal Enrichment

Animals were socially housed for psychological/environmental enrichment and provided with items such as a small amount (handful) of shredded paper in each cage.

It is considered that there were no known contaminants in the enrichment that could have interfered with the outcome of the study.

4.5.6.3. Environmental Conditions[1]

The targeted conditions for animal room environment were as follows:

Temperature:	19°C to 25°C
Humidity:	≥ 35%
Light Cycle:	12 hours light and 12 hours dark (except during any designated procedures)
Ventilation:	10 or more air changes per hour

Environmental conditions were within the targets throughout the study.

4.5.6.4. Food

Diet:	Complete rodent diet (Reference No. A04C-12)
Type:	Pellets
Frequency/Ration:	Ad libitum, except during designated procedures
Analysis:	Diet is sterilized by irradiation and analyzed by the supplier. Each batch of diet is supplied with a certificate of analysis which is verified and authorized for release by a veterinarian, and kept on file at the Test Facility. It is considered that there were no known contaminants in the feed that would have interfered with the objectives of the study.

4.5.6.5. Water

Type:	Municipal tap water, softened and filtered (0.2 µm) mains drinking water
Frequency/Ration:	Freely available to each animal via an automatic watering system (except during designated procedures)
Analysis:	Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility. It is considered that there were no known contaminants in the water that could have interfered with the outcome of the study.

4.5.6.6. Veterinary Care

Veterinary care was available throughout the course of the study, and animals were examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations and recommended therapeutic treatments were documented in the study records and reviewed by the Study Director.

Male No. 1015 (vehicle control group) was given local care (talc) from Day 28 to Day 39 due to a skin lesion (right forelimb).

[1] On Day 46, the fire alarm of the animal unit sounded for 4 minutes and the ventilation was interrupted at the same time. These events of short duration had no noticeable impact on the global health status of the animals.

4.6. Experimental Design

Text Table 6
Experimental Design

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume[a] (mL/kg)	Dose Concentration (mg/mL)	Animal Nos.			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Vehicle control	0	10	0	1001 to 1010	1501 to 1510	1011 to 1015	1511 to 1515
2	Test item	500	10	50	2001 to 2010	2501 to 2510	-	-
3	Test item	1000	10	100	3001 to 3010	3501 to 3510	-	-
4	Test item	2000	10	200	4001 to 4010	4501 to 4510	4011 to 4015	4511 to 4515

- = Not applicable.
[a] Based on the most recent body weight measurement.

4.6.1. Administration of Test Materials

Route of Administration: Oral (gavage)

Treatment Frequency: Daily

Treatment Duration: At least 90 days

Method: The first day of dosing was designated as Day 1.
Dose formulations were stirred at receipt and continuously during dosing.
Doses were given by gavage using a syringe with attached cannula.
On few occasions, animals were partially dosed (actual volume administered unknown, small to moderate amount of formulation lost). Details are kept in the raw data. In view of the small number of occasions (10 in total, between Day 4 and Day 87, on different animals) and considering that the dose regimen is daily during 13 weeks, this event was not considered to have impacted the study integrity or the study conclusions.

4.6.2. Justification of Route and Dose Levels

The oral route of administration was selected because this is the route of administration specified in the OECD 408 and OCSPP guidelines. The dose levels were set by the Study Director in agreement with the Study Monitor based on the available information of the chemical nature and characteristics of the test item, and available data and information from previous experimental work, including the results of a dose range finding (DRF) study (Study Code No. 21/300-101PE). Based on those results where the test item was given at 500, 1000, and 2000 mg/kg/day in distilled water, 2000 mg/kg/day was selected as the high dose for this study. The low and intermediate dose levels of 500 and 1000 mg/kg/day were selected to derive a dose-response for any effects that may have been observed.

4.7. In-Life Procedures, Observations, and Measurements

The in-life procedures, observations, and measurements listed below were performed.

Text Table 7
General In-Life Assessments - Main and Recovery Study Animals

Parameter	Population(s)	Frequency	Comments
Mortality	All main and recovery animals	At least twice daily[a] (morning and end of the working day) beginning upon arrival through termination/release	Animals observed within their cage unless necessary for identification or confirmation of possible findings.
Cageside observations	All main and recovery animals	Before and at least once after dosing on dosing days At least once daily on non-dosing days, from Week -1[b]	Animals observed within their cage unless necessary for identification or confirmation of possible findings.
Detailed clinical observations	All main and recovery animals	Weekly; from Week -1 and throughout the study	Animals removed from the cage.
Arena observations	All main and recovery animals	Once before the first administration and at least weekly thereafter	Animals observed for specific clinical signs in a standard arena, see Individual Data Explanation Page.
Individual body weights	All main and recovery animals	Weekly from Week -1 and throughout the study	Last body weight before terminal fasting
Food consumption	All main and recovery animals	Weekly for each cage of animals from Day 1 and throughout the study	Quantitatively measured
Behavioral functional observational battery (FOB)	5 main animals/sex/group	On a suitable day during Week 13, before dosing	As detailed in the section below
Locomotor activity test (Motor Monitor Test)			
Ophthalmology	All main and recovery animals (including alternate animals pretest)	Once pretest (all animals) At the end of the dosing period (Week 13 - Groups 1 and 4 main animals only)	See details in the section below
Estrous cycle	All main and recovery females	On the day of necropsy	See details in the section below

[a] Except on days of receipt and necropsy where frequency was at least once daily.
[b] For observations that could not be attributed to an individual animal due to social housing, the observation was noted to each animal in the socialized group.

4.7.1. Behavioral Functional Observational Battery (FOB)

Behavioral tests were conducted in group-housed animals.

FOB parameters were evaluated per Test Facility SOPs, as follows:

- In a first step, the animal underwent neurobehavioral evaluation in the home cage with ranking of posture, palpebral closure, stereotypies, convulsions, and tremors.
- In a second step, the ease of removal of the animal from the home cage and its reactivity to handling during removal and transfer to the open field were scored.
- In a third step, the animal was placed in a 50 x 50 x 20 cm black open field and observed for 2 minutes in freely moving conditions. Arousal, vocalizations, respiration, gait, stereotypies, convulsions, and tremors were ranked. The number of rearing occasions was counted.
- At the end of the 2-minute observation period, defecation (aspect of feces) was ranked and the animals underwent a series of additional observations and tests (from the least to the most invasive).

- The observer handled the animal and ranked fur appearance, lacrimation, salivation, exophthalmos, palpebral closure, and erected fur (piloerection).
- The animal was tested for various reflexes such as response to a touch of the body with a rod, startle response (using a clicker), tail pinch response and pupil response.
- Body temperature was measured using a rectal probe.
- The animal was ranked for body tone, forelimbs and hindlimbs grip strength and air righting reflex (from a height of 30 cm). Forelimbs and hindlimbs grip strength was measured with a T-shaped bar connected to a dynamometer that determines the maximal force developed by the limbs when the operator pulls the animal away from the bar. The measure was performed 3 times (individual values of repeated measurements kept in the raw data but not reported) and the mean value was calculated and reported.

A detailed description of FOB measurements and scoring is presented in Appendix 15.

4.7.2. Locomotor Activity Test

A locomotor activity test was performed in an open field in order to assess reactivity to a novel environment and motor activity. Activity was monitored by a photobeam analysis system (Motor Monitor supplied by (b) (4)) for 1 hour. The arena is divided by 7 and 15 equally spaced infrared beams in width and length, respectively; the time and the number of beams interrupted by the animal were recorded. Motor activity is divided into 2 types of activity: ambulatory activity (large animal movements like walking) and fine movements (including grooming and head movements). The proportion of beams blocked by the rat in each type of activity was calculated.

4.7.3. Ophthalmic Examinations

A mydriatic agent was instilled into the eyes before examination. Examination of adnexa, optic media and fundus was performed by indirect ophthalmoscopy.

In the absence of test item-related ophthalmological findings, the examination of Group 2 and 3 animals at the end of the dosing period and of recovery animals at the end of the recovery period was judged unnecessary.

4.7.4. Estrous Cycles

On the day of necropsy, a vaginal smear was taken to determine the cycle stage and allow correlation with histopathology of female reproductive organs. The vaginal smears performed before necropsy were fixed with air-drying and ethanol. Once the cycle stage was determined, the vaginal smears were stained with hematoxylin and eosin (see Section 4.9.7).

4.8. Laboratory Evaluations

4.8.1. Clinical Pathology

4.8.1.1. Sample Collection

Samples were collected according to Text Table 8.

Text Table 8
Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	Urinalysis
1 to 4 (main animals only)	Day 91 or Day 92	X	X	X	X
1 and 4 (recovery animals only)	Day 120	X	X	X	X
Fasting (overnight, about 16 h):		-	-	Yes	Yes
Method/Comments:		Submental vein, sublingual vein under slight isoflurane anesthesia, or abdominal aorta immediately after euthanasia			Deprived of food Water ad libitum
Target Volume (mL):		0.5	0.9	1.0	As available
Anticoagulant:		EDTA-K_2	Trisodium citrate	None	-
Processing:		None	Plasma	Serum	-

X = Sample collected; - = Not applicable; h = Hours.

4.8.1.2. Hematology

Blood samples were analyzed for the parameters specified in Text Table 9.

Text Table 9
Hematology Parameters

Red blood cell count Hemoglobin concentration Hematocrit Mean corpuscular volume Red blood cell distribution width (gated) Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Mean platelet volume Reticulocyte count	Platelet count White blood cell count Neutrophil count Lymphocyte count Monocyte count Eosinophil count Basophil count Large unstained cells count

In addition, a blood smear was prepared from each hematology sample. Blood smears were labeled, stained, and stored. The smears were examined and results reported when deemed necessary during the analysis of samples, as required by Test Facility SOP.

4.8.1.3. Coagulation

Blood samples were processed for plasma, and plasma was analyzed for the parameters listed in Text Table 10.

Text Table 10
Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time

4.8.1.4. Clinical Chemistry

Blood samples were processed for serum, and the serum was analyzed for the parameters specified in Text Table 11.

Text Table 11
Clinical Chemistry Parameters

Alanine aminotransferase	Albumin
Aspartate aminotransferase	Globulin (calculated)
Alkaline phosphatase	Albumin/Globulin ratio
Total bilirubin	Glucose
Urea nitrogen/Urea	Cholesterol
Creatinine	High density lipoprotein
Calcium	Low density lipoprotein
Phosphorus	Triglycerides
Bile acids	Sodium
Total protein	Potassium
Gamma glutamyl transferase	Chloride

4.8.1.5. Urinalysis

Urine samples were processed and analyzed for the parameters listed in Text Table 12.

Text Table 12
Urinalysis Parameters

Volume	Glucose
Color	Bilirubin
Appearance/Clarity	Ketones
Specific gravity	Blood
pH	Osmolality
Nitrite	Sediment
Protein	

4.8.2. Bone Marrow Smear Evaluation

Bone marrow smears were collected and prepared as described in Text Table 16.

Evaluation of stained smears was not performed.

4.8.3. Thyroid Hormone Analysis

4.8.3.1. Sample Collection

Samples were collected according to Text Table 13.

Text Table 13
Samples for Thyroid Hormone Analysis

Group Nos.	Time Point	Hormone Analysis
1 to 4 (main animals only)	Day 91 or Day 92	X[a]
1 and 4 (recovery animals only)	Day 120	X[a]
Fasting (overnight, about 16 h):		Yes
Method/Comments:		Submental vein, or sublingual vein under slight isoflurane anesthesia
Target Volume (mL):		1.3
Anticoagulant:		None
Special Requirements:		Samples kept at room temperature for at least 30 minutes to allow clotting (maximum up to 2 hours)
Processing:		Serum

X = Sample collected; h = Hours.
[a] Between 7.00 a.m. and 10.30 a.m. because of diurnal variation of hormone levels.

4.8.3.2. Sample Processing

Samples were processed according to Text Table 14.

Text Table 14
Thyroid Hormone Sample Processing

Centrifugation	Volume Serum Aliquot 1[2]	Volume Serum Aliquot 2	Volume Serum Aliquot 3	Volume Serum Aliquot 4[3,4]	Freezing
1800 g 10 minutes Approximately +21°C	At least 150 µL	At least 150 µL	At least 100 µL	At least 100 µL	-80°C ± 10ºC

All aliquots were shipped in dry ice to the Test Site for analysis as described in Appendix 1.

Stability in rat serum: 132 days for T3 and T4, and 142 days for TSH when stored at a temperature set to maintain -80°C ± 10ºC.

4.8.3.3. Thyroid Hormone Sample Analysis

Thyroid hormone samples were analyzed at the Test Site for T3, T4 and TSH levels (Study Phase No. 21/300-430AN).

The methods and results are presented in Appendix 26.

4.9. Terminal Procedures

Terminal procedures are summarized in Text Table 15.

Text Table 15
Terminal Procedures - Main Animals

Group Nos.	Euthanasia Days	Necropsy Procedures			Histology Processing	Microscopic Evaluation
		Necropsy	Tissue Collection	Organ Weights		
1 and 4	91–92	X	Full list[a]	Full list[a]	Full list[a]	Full list[a]
2 and 3	91–92	X	Full list[a]	Full list[a]	Gross lesions	Gross lesions

X = Procedure conducted.
[a] See Text Table 16 for list of tissues applicable to each procedure.

Terminal Procedures - Recovery Animals

Group Nos.	Euthanasia Day	Necropsy Procedures			Histology Processing	Microscopic Evaluation
		Necropsy	Tissue Collection	Organ Weights		
1 and 4	120	X	Full list[a]	Full list[a]	Gross lesions	Gross lesions

X = Procedure conducted.
[a] See Text Table 16 for list of tissues applicable to each procedure.

4.9.1. Method of Euthanasia

Animals were euthanized by carbon dioxide inhalation followed by exsanguinatio

[2] Volume less than 150 µL for Male No. 2001 (500 mg/kg/day) on Day 91. There were consequently no Aliquots 2 to 4 for this animal.
[3] Volume less than 100 µL for Female Nos. 2504 (500 mg/kg/day) and 4504 (2000 mg/kg/day) on Day 91, Female No. 2508 (500 mg/kg/day) and Male No. 3008 (1000 mg/kg/day) on Day 92, and Male No. 4012 (2000 mg/kg/day) on Day 120.
[4] No aliquot could be obtained from Male No. 3001 (1000 mg/kg/day) due to insufficient serum volume.

4.9.2. Unscheduled Deaths

There were no unscheduled deaths during the course of the study.

4.9.3. Scheduled Euthanasia

Main and recovery animals were fasted overnight before necropsy and had a terminal body weight recorded. When applicable, animals were euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, were necropsied throughout the day.

4.9.4. Necropsy

Main and recovery animals were subjected to a complete necropsy examination, which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Necropsy procedures were performed by qualified personnel with appropriate training and experience in animal anatomy and gross pathology. A Veterinary Pathologist was available.

4.9.5. Organ Weights

The organs identified in Text Table 16 were weighed at necropsy for all animals. Paired organs were weighed together. Organ to body weight ratios (using the terminal body weight) and organ to brain weight ratios were calculated.

4.9.6. Tissue Collection and Preservation

Representative samples of tissues identified in Text Table 16 were collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated.

Text Table 16
Tissue Weighing, Collection, Processing, and Evaluation Table

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Animal ID	-	X	-	-
Artery, aorta	-	X	X	X
Body cavity, nasal	-	X	-	-
Bone marrow, sternum	-	X	X	X
Bone marrow smear	-	X[a]	-	-
Bone, femur	-	X (1)	X (1)	X (1)
Bone, sternum	-	X	X	X
Brain	X	X	X	X
Epididymis[e]	X (2)	X (2)[b]	X (2)	X (2)
Esophagus	-	X	X	X
Eye[5]	-	X (2)[b]	X (2)	X (2)
Ganglion, dorsal root, lumbar	-	X	-	-
Gland, adrenal	X (2)	X (2)	X (2)	X (2)
Gland, clitoral	-	X (2)	-	-
Gland, lacrimal	-	X (2) (extra-orbital)	-	-
Gland, Harderian	-	X (2)	X (1)	X (1)
Gland, mammary	-	X	X	X
Gland, parathyroid	[d]	X (2)	X (2)	X (2)
Gland, pituitary	X	X	X	X

[5] See Deviations in Appendix 1.

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Gland, preputial	-	X (2)	-	-
Gland, prostate	X	X	X	X
Gland, salivary, submandibular	-	X (2)	X (1)	X (1)
Gland, salivary, sublingual	-	X (2)	-	-
Gland salivary, parotid	-	X (2)	-	-
Gland, seminal vesicle with coagulating gland	X (2)	X (2)	X (2)	X (2)
Gland, thyroid	X (2)	X (2)	X (2)	X (2)
Gland, Zymbal's	-	X (2)	-	-
Gut-associated lymphoid tissue[c]	-	X	X	X
Heart	X	X	X	X
Joint, femorotibial	-	X (1)	X (1)	X (1)
Kidney	X (2)	X (2)	X (2)	X (2)
Large intestine, cecum	-	X	X	X
Large intestine, colon	-	X	X	X
Large intestine, rectum	-	X	X	X
Larynx	-	X	-	-
Liver	X	X	X	X
Lung	-	X	X	X
Lymph node, mandibular	-	X (2)	X (1)	X (1)
Lymph node, mesenteric	-	X	X	X
Macroscopic abnormalities	-	X	X	X
Muscle, skeletal	-	X (2)	X (1)	X (1)
Nerve, optic	-	X (2)[b]	X (2)	X (2)
Nerve, sciatic	-	X (2)	X (1)	X (1)
Nerve, tibial	-	X (2)	-	-
Ovary	X (2)	X (2)	X (2)	X (2)
Olfactory bulbs	-	X	X	X
Oviduct	-	X (2)	-	-
Pancreas	-	X	X	X
Skin	-	X	X	X
Small intestine, duodenum	-	X	X	X
Small intestine, ileum	-	X	X	X
Small intestine, jejunum	-	X	X	X
Spinal cord	-	X	X	X
Spleen	X	X	X	X
Stomach	-	X	X	X
Testis[e]	X (2)	X (2)[b]	X (1)	X (1)
Thymus	X	X	X	X
Tongue	-	X	X	X
Trachea	-	X	X	X

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Ureter	-	X (2)	-	-
Urinary bladder	-	X	X	X
Uterus/Cervix	X	X	X	X
Vagina	-	X	X	X
Vaginal smear	-	X	X	-

X = Procedure conducted; - = Not applicable; (1) = One side; (2) = Both sides.
Macroscopic abnormalities in the organs listed and in other organs were sampled at necropsy, processed for histology and examined microscopically.

[a] Two bone marrow smears were collected from the femur at necropsies (for possible examination). Bone marrow smears were allowed to air dry and then stained using the Aerospray automaton (May-Grünwald Giemsa method).

[b] Eyes and optic nerves were preserved in Davidson's fixative. Testes and epididymides were preserved in modified Davidson's fixative.

[c] From small intestine: Peyer's patch or solitary lymphoid follicle.

[d] Weighed with gland, thyroid.

[e] For terminal and recovery males, the left testis and epididymis were dedicated for sperm analysis, the right organs for the histopathological examination. Both testes and epididymis were weighed (separately) as well as the left cauda of the epididymis dedicated for sperm analysis. After sperm analysis, the remainder of the left epididymis was preserved.

4.9.7. Histology

Tissues identified in Text Table 16 (except animal identification, nasal cavities, bone marrow smears, lumbar ganglion dorsal root, clitoral glands, lacrimal glands, preputial glands, sublingual and parotid salivary glands, Zymbal's glands, larynx, tibial nerves, oviducts, and ureters) were embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

The same sampling and trimming procedures were used for all applicable tissues in all applicable dose groups.

A detailed qualitative examination was performed for the testes of Group 1 and 4 main males, taking into account the tubular stages of the spermatogenic cycle. In addition to the hematoxylin and eosin-stained slide, an additional slide stained with PAS was prepared and examined. The examination was conducted in order to identify treatment-related effects such as missing germ cell layers or types, retained spermatids, multinucleated or apoptotic germ cells and sloughing of spermatogenic cells into the lumen. Any cell- or stage-specificity of testicular findings were recorded.

Vaginal smears performed before necropsy were stained with hematoxylin and eosin after air-drying and ethanol fixation at the Test Facility.

4.9.8. Sperm Analysis

Sperm count and motility assessment was performed for Groups 1 to 4, using automated equipment ((b) (4)). The left cauda epididymis was sampled and used for the assessment of caudal sperm reserves and sperm motility, including progressive motility. Sperm counts were performed using the left testis following removal of the tunica albuginea.

Sperm morphology was evaluated for Groups 1 and 4 (at least 200 sperm per sample, where possible). The numbers of sperm with each type of abnormality were recorded. Slides for assessment of sperm morphology were prepared for all males from all groups. Evaluation was performed for the control and high dose groups in first instance.

4.9.9. Microscopic Evaluation

Histopathological evaluation was performed by a Veterinary Pathologist with training and experience in laboratory animal pathology.

Histopathological examination was performed for all gross lesions from animals in all groups, except those for which the diagnosis was judged unnecessary for the outcome of the study by the Pathologist.

4.9.10. Peer Review

A Pathology Peer Review was conducted according to internal procedures by another Pathologist at the Test Facility. The notes made during the Peer Review were archived with the study data. The Peer Review Statement is presented in Appendix 28.

5. STATISTICAL ANALYSIS

Any data collected during the predose period were tabulated, summarized, and statistically analyzed. All statistical analyses were performed within the respective study phase, unless otherwise noted. Numerical data collected on scheduled occasions from main and recovery animals were summarized and statistically analyzed as indicated below according to sex and occasion.

5.1. Constructed Variables

Body Weight Changes:	Calculated between each scheduled interval as well as between the following intervals: Days 1 to 90 and Days 90 to 119
Food Consumption:	Calculated between each scheduled interval (individual data only) and as specified above for body weight gains
Organ Weight Relative to Body Weight:	Calculated against the terminal body weight for scheduled intervals
Organ Weight Relative to Brain Weight:	Calculated against the brain weight for scheduled intervals

5.2. Descriptive Statistical Analyses

Means, standard deviations (or % coefficient of variation or standard error, when deemed appropriate), ratio, percentages, numbers, and/or incidences were reported as appropriate by dataset.

5.3. Inferential Statistical Methods

All statistical tests were conducted at the 5% significance level. All pairwise comparisons were conducted using two-sided tests and reported at the 1% and 5% levels, unless otherwise noted.

The pairwise comparisons of interest are listed below:

Group 2	vs.	Group 1
Group 3	vs.	Group 1
Group 4	vs.	Group 1

Analyses were performed according to the matrix below when possible, but excluded any group with less than 3 observations.

Text Table 17
Statistical Matrix

Variables for Inferential Analysis	Statistical Method	
	Parametric/Non-Parametric	Non-Parametric
Body weight	X	-
Body weight gains	X	-
Food consumption	X	-
Hematology variables	X	-
Coagulation variables	X	-
Clinical chemistry variables	X	-
Urinalysis variables	X	-
Thyroid hormones	X	-
FOB quantitative variables	X	-
FOB qualitative variables	-	-
Locomotor activity variables	X	-
Organ weights	X	-
Organ weight relative to body weight	X	-
Organ weight relative to brain weight	X	-
Sperm morphology	-	X
Sperm count and motility	X	-

X = Statistical method used; - = Statistical method not used.

5.4. Parametric/Non-Parametric

Levene's test was used to assess the homogeneity of group variances.

Groups were then compared using an overall one-way ANOVA F-test if Levene's test was not significant or the Kruskal-Wallis test if it was significant. If the overall F-test or Kruskal-Wallis test was found to be significant, then pairwise comparisons were conducted using Dunnett's or Dunn's test, respectively.

5.5. Non-Parametric

The 2 groups were compared using a Dunn's test.

5.6. Data Generated Outside (b) (4)

Thyroid hormone data, sperm count and motility data and (b) (4) data were analyzed using a (b) (4) software package. Levene's test was used to test the equality of variance across groups and Shapiro-Wilk's test was used to assess the normality of the data distribution in each group. Data with homogeneous variances and normal distribution in all groups were analyzed using ANOVA followed by Dunnett's test.

Data showing non-homogeneous variances or a non-normal distribution in at least 1 group were analyzed using Kruskal-Wallis test followed by the Wilcoxon's rank sum test.

For datasets intended to include only 2 groups, Levene's test was used to test the equality of variance across groups and Shapiro Wilk's test was used to assess the normality of the data distribution in each group. Data with homogeneous variances and normal distribution in all groups were analyzed using the Student's t-test. Data showing non-homogeneous variances or a non-normal distribution in at least 1 group were analyzed using the Wilcoxon's rank sum test.

6. COMPUTERIZED SYSTEMS

Critical computerized systems used in the study are listed below or presented in the appropriate Phase Report. All computerized systems used in the conduct of this study have been validated; when a particular system has not satisfied all requirements, appropriate administrative and procedural controls were implemented to assure the quality and integrity of data.

Text Table 18
Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Vaisala (ViewLinc EMS)	Environmental monitoring system
(b) (4)® (including Dispense)	Test item receipt, accountability and/or formulation activities; in-life; clinical pathology; postmortem; statistical analysis
(b) (4)®	Safety assessment document management and publishing Collection of 21 CFR Part 11 compliant signature
(b) (4)	Electronic signatures
	Deviation information library
	Statistical analysis
	Locomotor activity test
	Sperm analyser
	Hematology parameters (interfaced to (b) (4)
	Coagulation parameters (interfaced to
	Coagulation parameters (interfaced to
	Biochemistry parameters (interfaced to
	Urine parameters (interfaced to (b) (4)
	Sample tracking

(b) (4) (Version 2003 or higher) was employed to present certain results and perform associated calculations.

7. RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND SPECIMENS

Study-specific raw data, documentation, retained samples and specimens, from this study were archived at the Test Facility archive by no later than the date of Final Report issue and kept for a period of 15 years following the date of issue of the Final Report.

Electronic data collected using (b) (4)s® (including Dispense), Study Director communication (e-mails) and documentation managed on (b) (4)s®, Study Plan, Study Plan amendments, and Final Report stored on (b) (4)®, and deviations were archived at the (b) (4) facility location in (b) (6).

Watson data are electronically archived at the (b) (4) facility location in (b) (6)

Disposition of residual/retained analytical samples was as described in the table below.

Text Table 19
Disposition of Residual/Retained Samples

Sample Type	Disposition
Analytical (and test item used in analysis)	Discarded
Thyroid hormones	Discarded

Archival location of all records, retained samples and specimens, and reports generated from phases performed by subcontractors is detailed in the applicable PI Reports.

Original Study Plan and amendments signed by the Sponsor (e-signed documents) were maintained at (b) (4) facility location in (b) (6).

8. RESULTS

8.1. Dose Formulation Analyses

(Appendix 3)

The actual concentrations of the test formulations varied between 96% and 106% of nominal concentrations. The test formulation samples stored at frozen were within the acceptable range of the concentration analysis (100% ± 15% of the measured concentration compared to the nominal concentration). The homogeneity of the 50 and 200 mg/mL of test samples were examined by measurement of the duplicate sampling of top, middle, and bottom locations of the formulations on the first analytical occasion. In case of the replicates sent for the homogeneity testing, the relative standard deviation was ≤ 2.4%. The highest relative standard deviation of the replicates was ≤ 4.0%, showing the homogeneity of all the samples. The acceptable criterion of the homogeneity was RSD% ≤ 10%.

On the second formulation analysis, the prepared formulations were sampled twice: firstly, right after the preparation, secondly 8 days after the preparation, applying constant stirring during the 8 days. The test item concentration of the formulations did not show significant differences, both sampling was within the acceptable ranges. Based on the result, the stability of the formulations under continuous stirring for 8 days was confirmed.

The formulation analyses were performed under appropriate analytical conditions.

In summary, the formulation analyses demonstrated homogeneous and accurate sample concentrations were used in the 90-day toxicity study in rats.

8.2. Mortality

(Appendix 4)

There was no unscheduled death during the study.

8.3. Clinical Observations

(Table 1, Table 2, Appendix 5, and Appendix 6)

Slight to severe salivations were noted for treated animals at all dose levels on Day 17 or 24, Day 45, and Day 73 (salivation control was realized at 3-week intervals at the request of the Study Director). Salivation affected all animals in each treated group and was associated with salivation-associated sign such as pedaling and/or ploughing at 1000 and/or 2000 mg/kg/day on Day 17 and at all dose levels on Days 45 and 73. These behaviors were noted with a dose-related incidence, mainly for males. Salivation and associated behaviors were transiently noted 5 minutes after the administration.

They were considered L-tryptophan (TRP Pro)-related but non-adverse. They were not noted thereafter during the recovery period.

Any other observations such as tail bent, thin cover or staining of the fur, skin lesion, skin scab and broken teeth were observed sporadically during pretest and/or dosing periods and were therefore considered incidental.

8.4. Arena Observations

There were no L-tryptophan (TRP Pro)-related clinical signs noted during the weekly arena observations.

8.5. Body Weights and Body Weight Gains

(Figure 1, Figure 2, Table 3, Table 4, and Appendix 7)

When compared with the control group, there was a slightly lower body weight gain in males given 1000 mg/kg/day and above from Day 16 to Day 36. This was not noted thereafter. The overall body weight gain was comparable for both sexes and between all groups over the dosing period (Day 1 to Day 90) and between Groups 1 and 4 during the recovery period (Day 90 to Day 119). This was not considered adverse in view of the transient occurrence and low magnitude of the change.

Text Table 20
Summary of Body Weight Gains (g)

Sex	Male				Female			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose Level (mg/kg/day)	**0**	**500**	**1000**	**2000**	**0**	**500**	**1000**	**2000**
Day 1 to Day 90	249.7 ± 20.9	245.2 ± 29.9	221.5 ± 34.8	232.5 ± 29.5	110.5 ± 21.2	116.0 ± 12.8	120.7 ± 17.8	119.3 ± 13.1
Day 90 to Day 119	17.4 ± 3.8	N.A.	N.A.	9.8 ± 8.8	0.6 ± 9.9	N.A.	N.A.	-1.8 ± 7.0

N.A. = Not applicable.

When compared with the control values, there was a slight decrease in male body weights over the dosing period at 1000 mg/kg/day on Day 90. The body weight was similar between control and animals given 2000 mg/kg/day at the end of the recovery period. This was not considered adverse in view of the low magnitude of the change.

Text Table 21
Summary of Body Weights (g)
(Percentage Difference from Control Group in Brackets)

Sex	Male				Female			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose Level (mg/kg/day)	**0**	**500**	**1000**	**2000**	**0**	**500**	**1000**	**2000**
Day 90	439.6 ± 26.3	424.9 ± 23.6 (-3.3%)	405.5 ± 34.1* (-7.8%)	418.1 ± 32.9 (-4.9%)	263.9± 26.2	266.3 ± 15.9 (+0.9%)	276.4 ± 17.5 (+4.7%)	273.9 ± 18.7 (+3.8%)
Day 119	451.8 ± 23.5	N.A.	N.A.	425.8 ± 27.9 (-5.8%)	279.2± 19.5	N.A.	N.A.	271.6 ± 11.8 (-2.7%)

N.A. = Not applicable; * = $p \leq 0.05$.

8.6. Food Consumption

(Table 5 and Appendix 8)

When compared with the control group, there was a slightly lower food consumption in males given 1000 mg/kg/day over the dosing period (Day 1 to Day 90) while the food intake was slightly higher in treated females at 1000 mg/kg/day and above. Food consumption was similar at 2000 mg/kg/day and in the control group in males and still slightly higher in females over the recovery period (Day 90 to Day 119). This was not considered adverse.

Text Table 22
Summary of Food Consumption (g/animal/day)
(Percentage Difference from Control Group in Brackets)

Sex	Male				Female			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose Level (mg/kg/day)	**0**	**500**	**1000**	**2000**	**0**	**500**	**1000**	**2000**
Day 1 to Day 90	25.3± 0.8	25.0 ± 1.0 (-1.5%)	23.5 ± 1.4 (-7.3%)	25.4 ± 2.5 (+0.1%)	18.3 ± 0.8	18.9 ± 0.5 (+3.2%)	19.6 ± 0.1 (+7.1%)	19.7 ± 0.7 (+7.8%)
Day 90 to Day 119	24.8± 0.7	N.A.	N.A.	24.3 ± 0.4 (-1.7%)	18.2	N.A.	N.A.	19.5 (+7.2%)

N.A. = Not applicable.

8.7. Behavioral Functional Observational Battery

(Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Appendix 9, Appendix 10, Appendix 11, Appendix 12, Appendix 13, and Appendix 14)

In Week 13, no relevant effects were noted on any neurobehavioral parameters, when compared with the vehicle control group.

Of note, 1 male dosed at 500 mg/kg/day was scored as slow for arousal in the open field and then had an abnormal behavior during the air righting reflex (felt on his back and rolled over before going back on limbs). This observation is an isolated event observed at the mid dose in 1 animal only. Thus, it is considered incidental and not related with the L-tryptophan (TRP Pro) administration.

Some animals in all groups, including the vehicle control group, walked on the rim of the open field for various durations or froze during the open field. As this is considered a normal exploratory behavior in a rat placed in the FOB environment and was not associated with other modifications of FOB parameters, these findings were therefore considered as incidental, unrelated to L-tryptophan (TRP Pro) administration.

Note: additional examinations of recovery animals at the end of the recovery period was judged unnecessary.

In conclusion, oral administration of L-tryptophan (TRP Pro) at 500, 1000, or 2000 mg/kg/day did not affect the parameters evaluated in the FOB examination in male and female rats when evaluated during Week 13, before dosing.

8.8. Locomotor Activity

(Figures 3, Table 12, and Appendix 16)

There was no consistent trend across the intervals or amongst the groups for either sex to suggest any effect of the treatment on motor activity and habituation to a novel environment of the treated animals, at any dose level. The percentage of habituation to a novel environment was comparable in all groups and/or consistent with the historical control data range.

8.9. Ophthalmic Examinations

(Appendix 17)

There were no L-tryptophan (TRP Pro)-related ophthalmic findings, at the end of the dosing period.

The ophthalmic findings observed in the main high dose group, given 2000 mg/kg/day, in Week 13, mainly consisted of corneal opacities noted as punctiform (pinpoint) or linear, focal or multifocal and of slight severity, and isolated persistence of pupillary membrane.

These findings were considered to be incidental since they were generally noted also in controls and/or were present from pretest. Moreover, all the observed findings are known to be observed in the laboratory rat as spontaneous, common, or congenital changes and can evolve with the time.

Moreover, slightly pale fundus or/and pale vessels in fundus were observed in half of the examined main females, given 2000 mg/kg/day. This visual pallor was not associated with any changes in the red blood cell parameters and/or other associated clinical signs for the concerned females, and was not observed in any high dose group male. This finding of a low severity was, thus, considered without any toxicological relevance.

8.10. Hematology

(Table 13 and Appendix 18)

There was no L-tryptophan (TRP Pro)-related change in hematology parameters at the end of the dosing and recovery periods.

When compared with control values, a decrease in white blood cell count (mainly neutrophils - up to -34%) was noted in treated males at the end of the dosing period, without a dose-related trend. However individual values of treated animals were within the historical control data range (except for 1 animal - Male No. 3001), therefore this change was not considered as biologically relevant.

Any other changes in hematology parameters were due to isolated variations and were therefore considered incidental.

8.11. Coagulation

(Table 14 and Appendix 19)

At the end of the dosing period (Day 91), a slightly elongated prothrombin time (PT) was noted in males treated at 2000 mg/kg/day (+9% vs. control) and a shortened activated partial thromboplastin time (APTT) was noted in females treated at 1000 mg/kg/day and above (up to -13% vs. control). The above-mentioned changes were of low magnitude and were therefore not considered adverse.

No change in coagulation parameters was noted at the end of the recovery period at 2000 mg/kg/day in both sexes, indicative of a full recovery.

Any other changes in coagulation parameters were due to isolated variations and were therefore considered incidental.

8.12. Clinical Chemistry

(Table 15 and Appendix 20)

There was no L-tryptophan (TRP Pro)-related change in clinical chemistry parameters at the end of the dosing period. There were minimal changes in phosphorus, creatinine, alanine aminotransferase activity (ALT), aspartate aminotransferase activity (AST), and potassium concentrations in either sexes at 1000 and/or 2000 mg/kg/day. Nevertheless the individual values of these parameters were within the historical control data range and therefore were not considered L-tryptophan (TRP Pro)-related.

Slightly lower albumin (and albumin/globulin ratio) and total protein concentrations were noted at the end of the recovery in females. This was not considered adverse in view of the low amplitude of the changes.

Any other changes in clinical chemistry parameters were due to isolated variations and were therefore considered incidental.

8.13. Urinalysis

(Table 16 and Appendix 21)

When compared with mean control value, a lower pH was noted in urine from treated animals. This appeared dose related and was more pronounced in males than in females. This was not noted at the end of the recovery period.

Any other changes in urine parameters were due to isolated variations and were therefore considered incidental.

Text Table 23
Summary of Urine pH

Sex	Male				Female			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose Level (mg/kg/day)	**0**	**500**	**1000**	**2000**	**0**	**500**	**1000**	**2000**
pH								
Day 91	7.80 ± 0.67	7.40 ± 0.70	6.70 ± 0.54**	5.45 ± 0.50**	6.95 ± 0.72	6.65 ± 0.63	6.40 ± 0.61	5.75 ± 0.35**

** = $p \leq 0.01$.

8.14. Estrous Cycle Stage at Necropsy

(Appendix 22)

There was no L-tryptophan (TRP Pro)-related perturbation of the estrous cycle for the females.

8.15. Sperm Count and Motility

(Table 17 and Appendix 23)

When compared with the control group, there was no change in the sperm count and motility from the testis and epididymis in treated males, at any dose level.

8.16. Sperm Morphology

(Table 18 and Appendix 24)

When compared with the control group, there was no change in the sperm morphology evaluation in treated males, at any dose level.

8.17. Thyroid Hormones

(Appendix 26)

When compared with the control group, there was no consistent trend amongst the treated groups for either sex to suggest any effect of the treatment on T3, T4, or TSH hormone analysis. L-tryptophan (TRP Pro) at 500, 1000, or 2000 mg/kg/day did not affect the hormones evaluated at the end of the dosing, or recovery period.

8.18. Gross Pathology

(Appendix 27)

8.18.1. Terminal Euthanasia Animals (Day 91/92)

No L-tryptophan (TRP Pro)-related gross findings were noted.

The gross findings observed were considered incidental, of the nature commonly observed in this strain and age of rat, and/or were of similar incidence in control and treated animals and, therefore, were considered unrelated to administration of L-tryptophan (TRP Pro).

8.18.2. Recovery Euthanasia Animals (Day 120)

No L-tryptophan (TRP Pro)-related gross findings were noted.

The gross findings observed were considered incidental, of the nature commonly observed in this strain and age of rat and/or were of similar incidence in control and treated animals and, therefore, were considered unrelated to administration of L-tryptophan (TRP Pro).

8.19. Organ Weights

(Appendix 27)

8.19.1. Terminal Euthanasia Animals (Day 91/92)

No L-tryptophan (TRP Pro)-related organ weight changes were noted.

There were isolated organ weight values statistically different from their respective controls.

There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. In addition, no histological findings were accounted for these weight variations. Thus, the organ weight differences observed were considered incidental or related to terminal body weight differences and unrelated to administration of L-tryptophan (TRP Pro).

8.19.2. Recovery Euthanasia Animals (Day 120)

No L-tryptophan (TRP Pro)-related organ weight changes were noted.

Occasional organ weight values were statistically different from their respective controls. However, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, the organ weight differences observed were considered incidental and/or related to terminal body weight differences and unrelated to administration of L-tryptophan (TRP Pro).

8.20. Histopathology

(Appendix 27)

8.20.1. Terminal Euthanasia Animals (Day 91/92)

There was no evidence of L-tryptophan (TRP Pro)-related microscopic findings in examined tissues.

The microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of Wistar Han IGS rat, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered unrelated to administration of L-tryptophan (TRP Pro).

8.20.2. Recovery Euthanasia Animals (Day 120)

There was no evidence of L-tryptophan (TRP Pro)-related microscopic findings in gross lesions examined at recovery euthanasia (Day 120).

9. CONCLUSION

In conclusion, administration of L-tryptophan (TRP Pro) by once daily oral gavage was well tolerated in rats at levels up to 2000 mg/kg/day. Clinical observations were limited to non-adverse salivations with associated pedaling and ploughing reflexes noted at ≥ 1000 mg/kg/day. There were non-adverse changes noted on body weights and food consumption at ≥ 1000 mg/kg/day as well as non-adverse coagulation parameter and urine pH changes at ≥ 1000 mg/kg/day. There were no gross lesions, organ weight changes, and evidence of treatment-related microscopic findings at necropsy. Based on these results, the no observed adverse effect level (NOAEL) was considered to be 2000 mg/kg/day.

Sponsor Reference No. (b) (4)

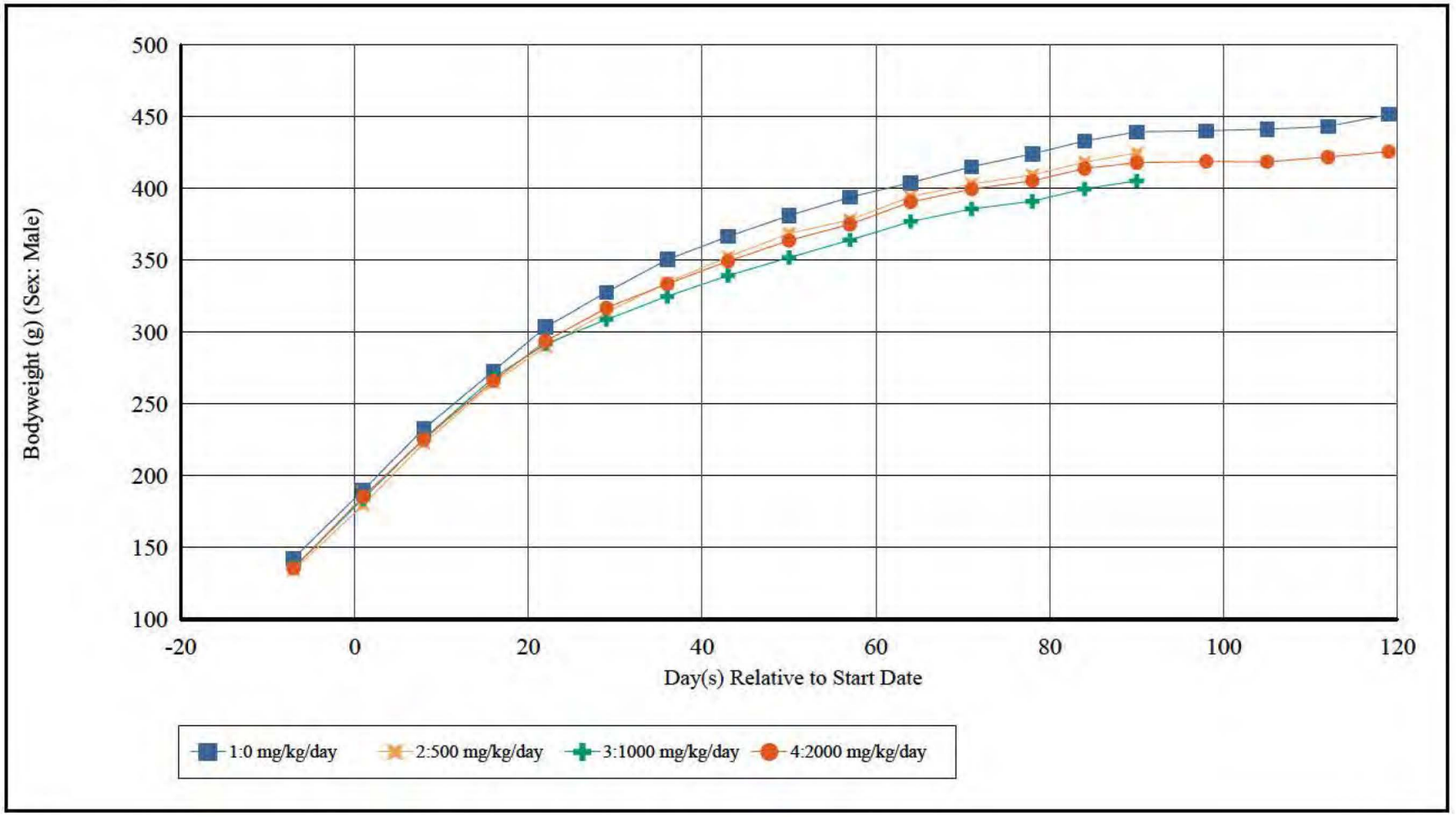
Test Facility Study No. (b) (4)

Figure 1

24-Feb-2023 08:42:43

Summary of Group Mean Body Weights: Males

(b) (4)



Sponsor Reference No. (b) (4)

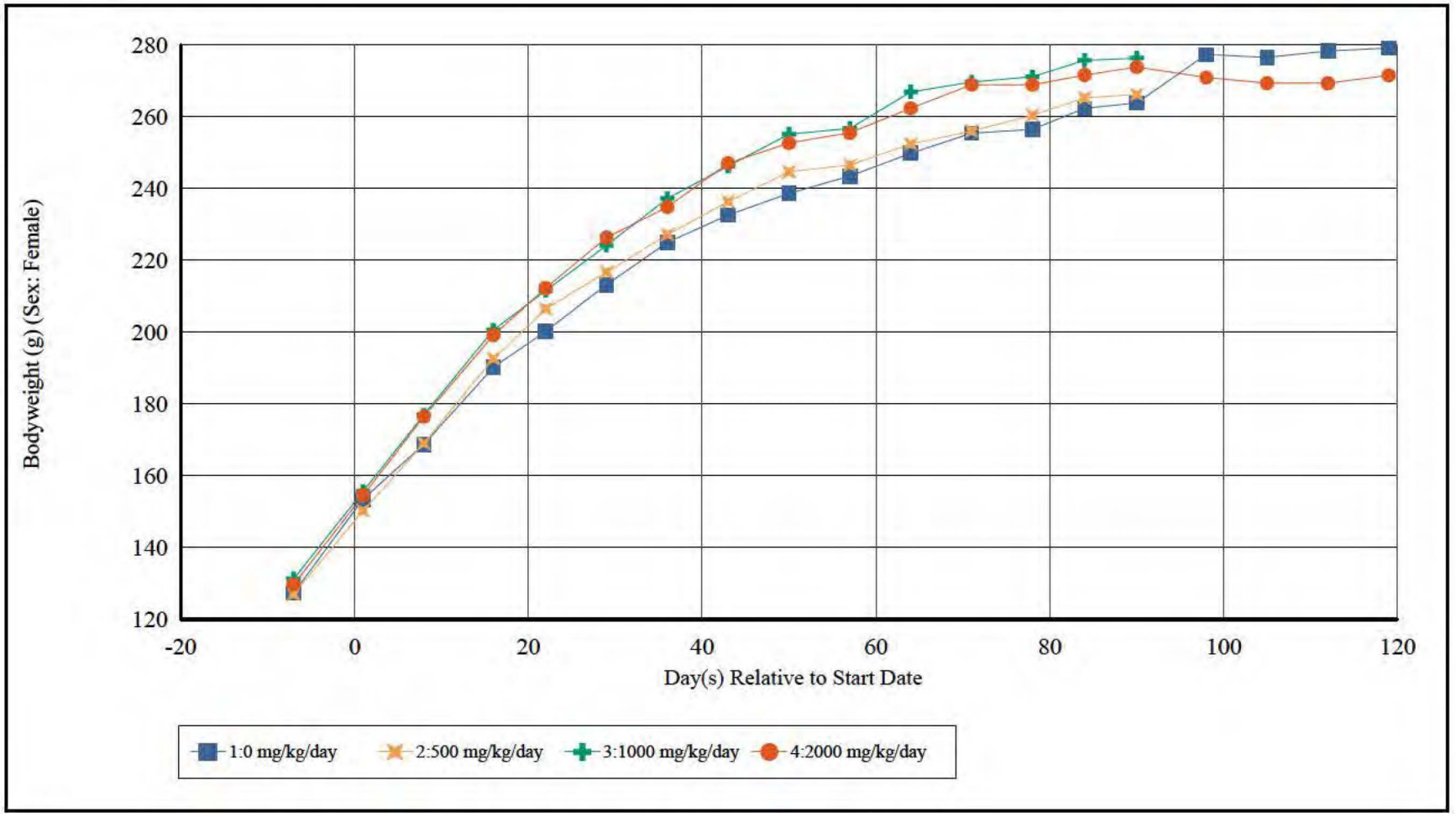
Test Facility Study No. (b) (4)

Figure 2

24-Feb-2023 08:42:14

Summary of Group Mean Body Weights: Females

(b) (4)

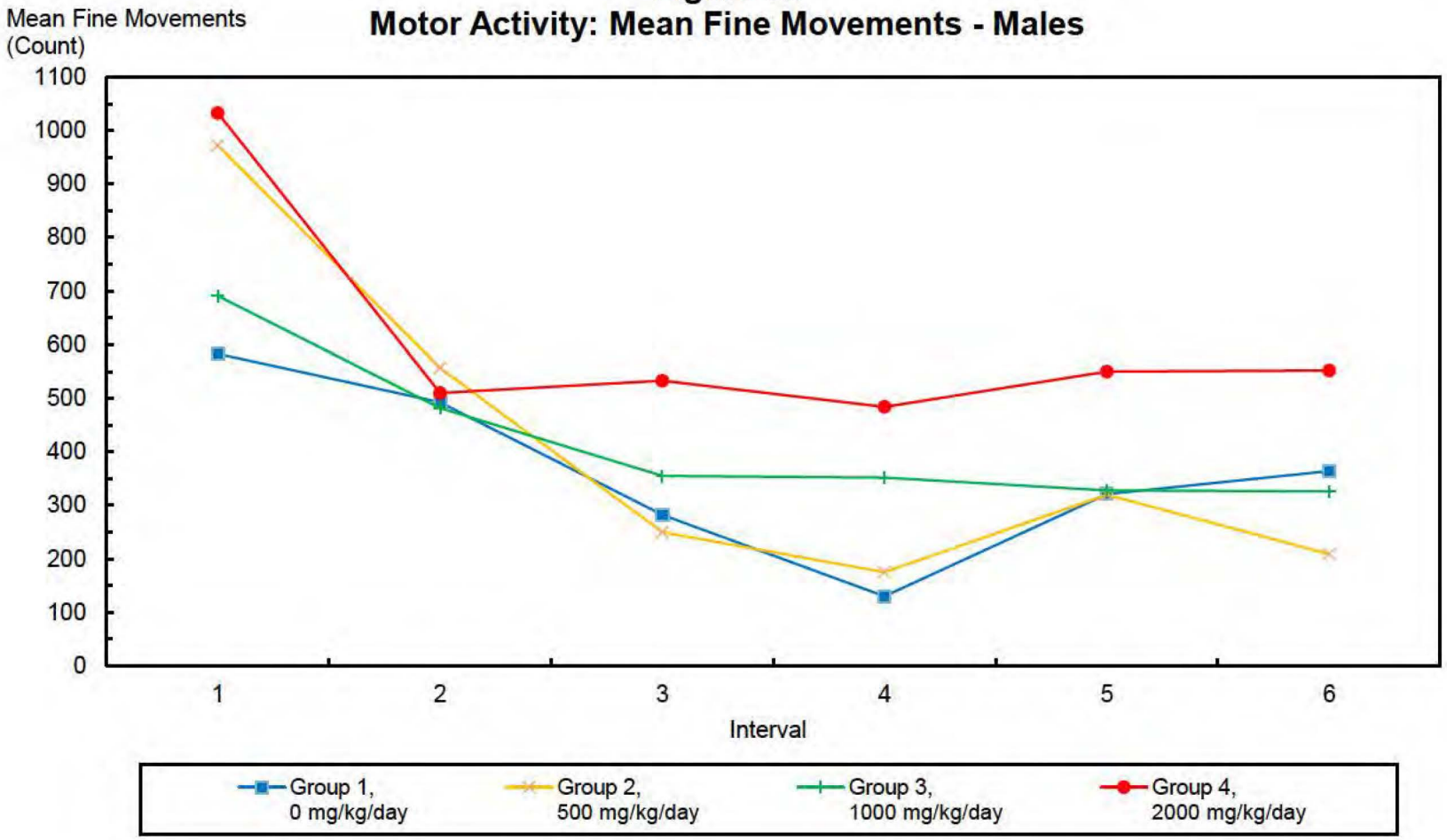


Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Figures 3

(b) (4)

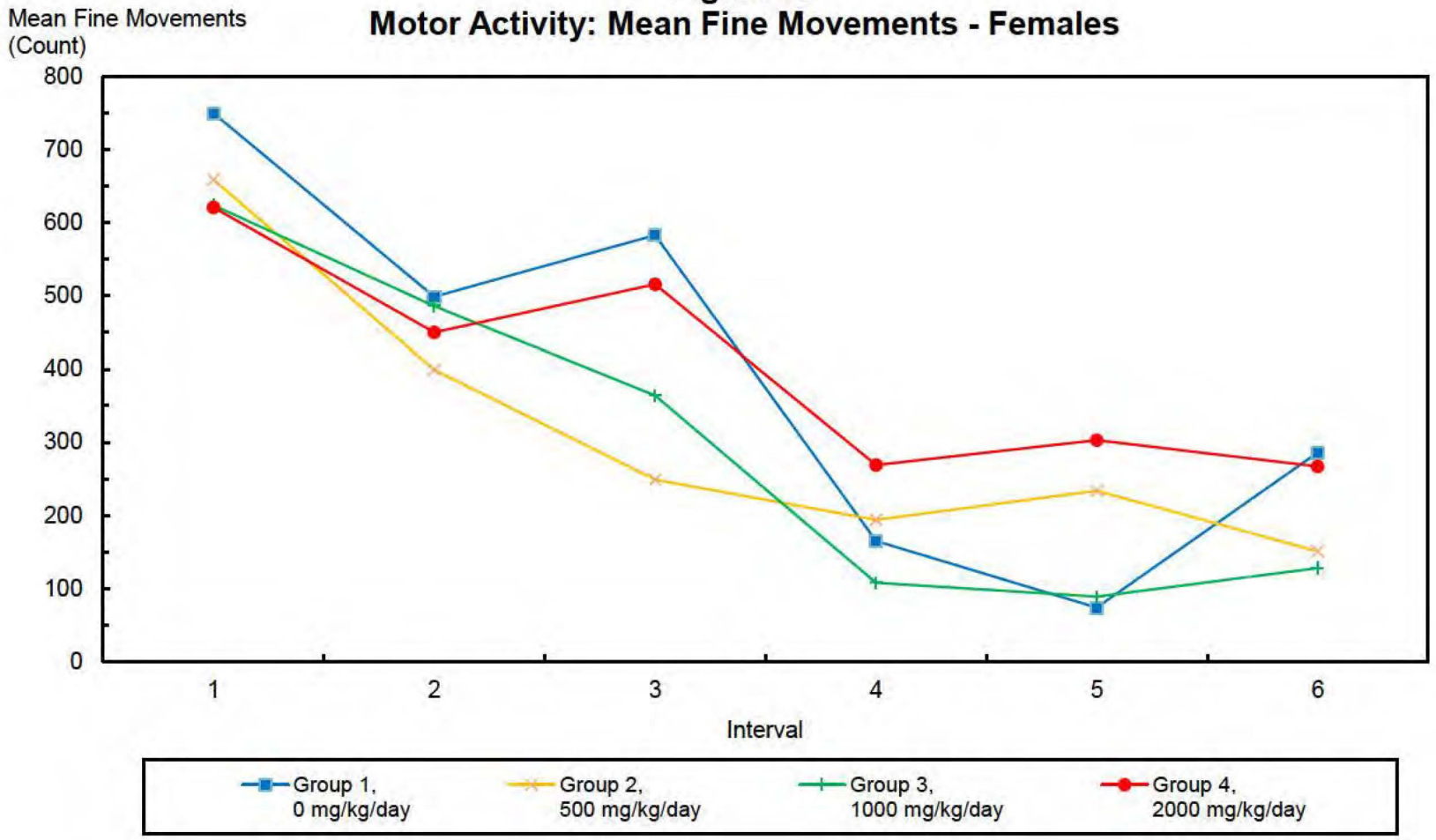
Figure 3a
Motor Activity: Mean Fine Movements - Males



Figures 3

(b) (4)

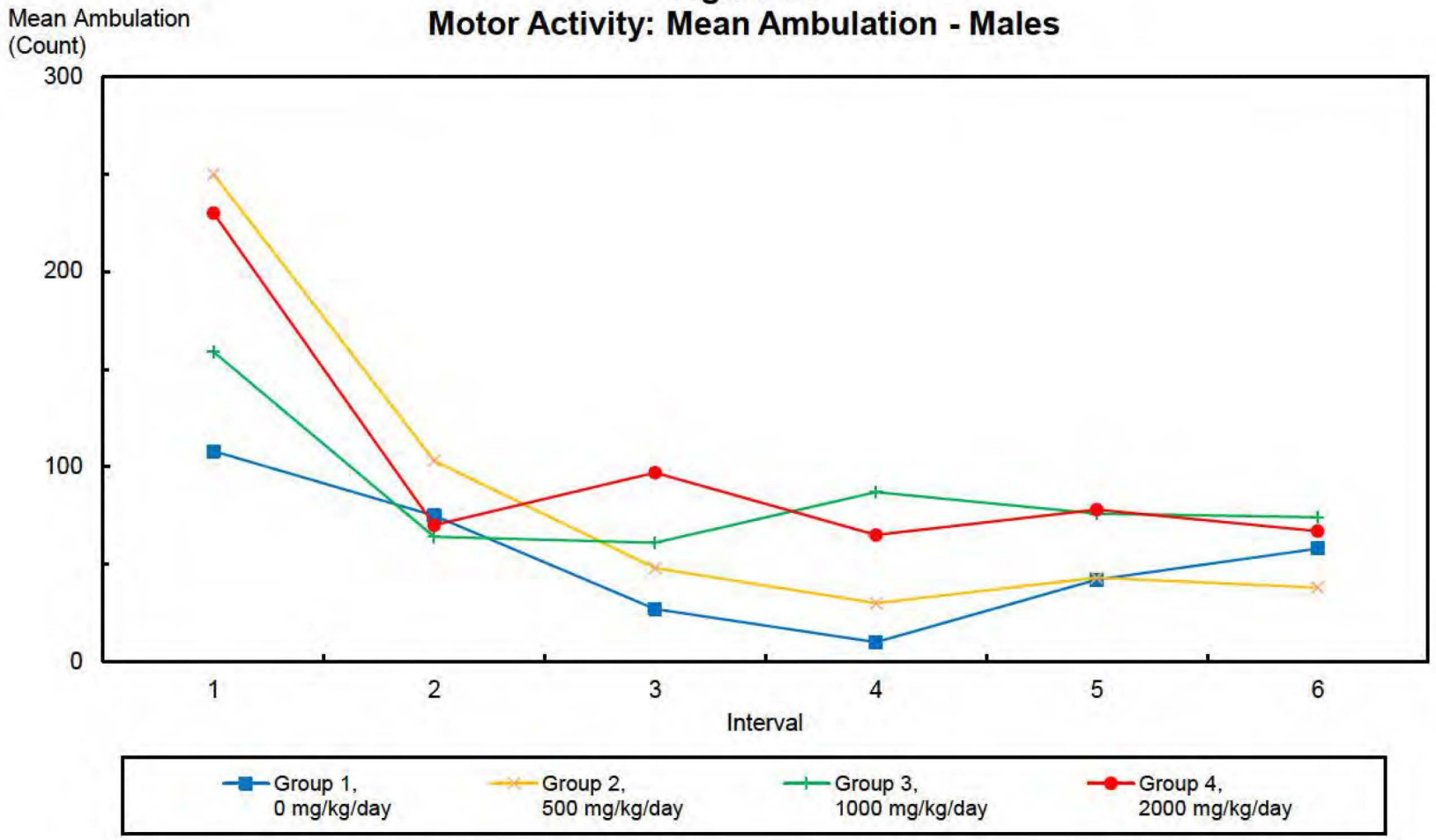
Figure 3b
Motor Activity: Mean Fine Movements - Females



Figures 3

(b) (4)

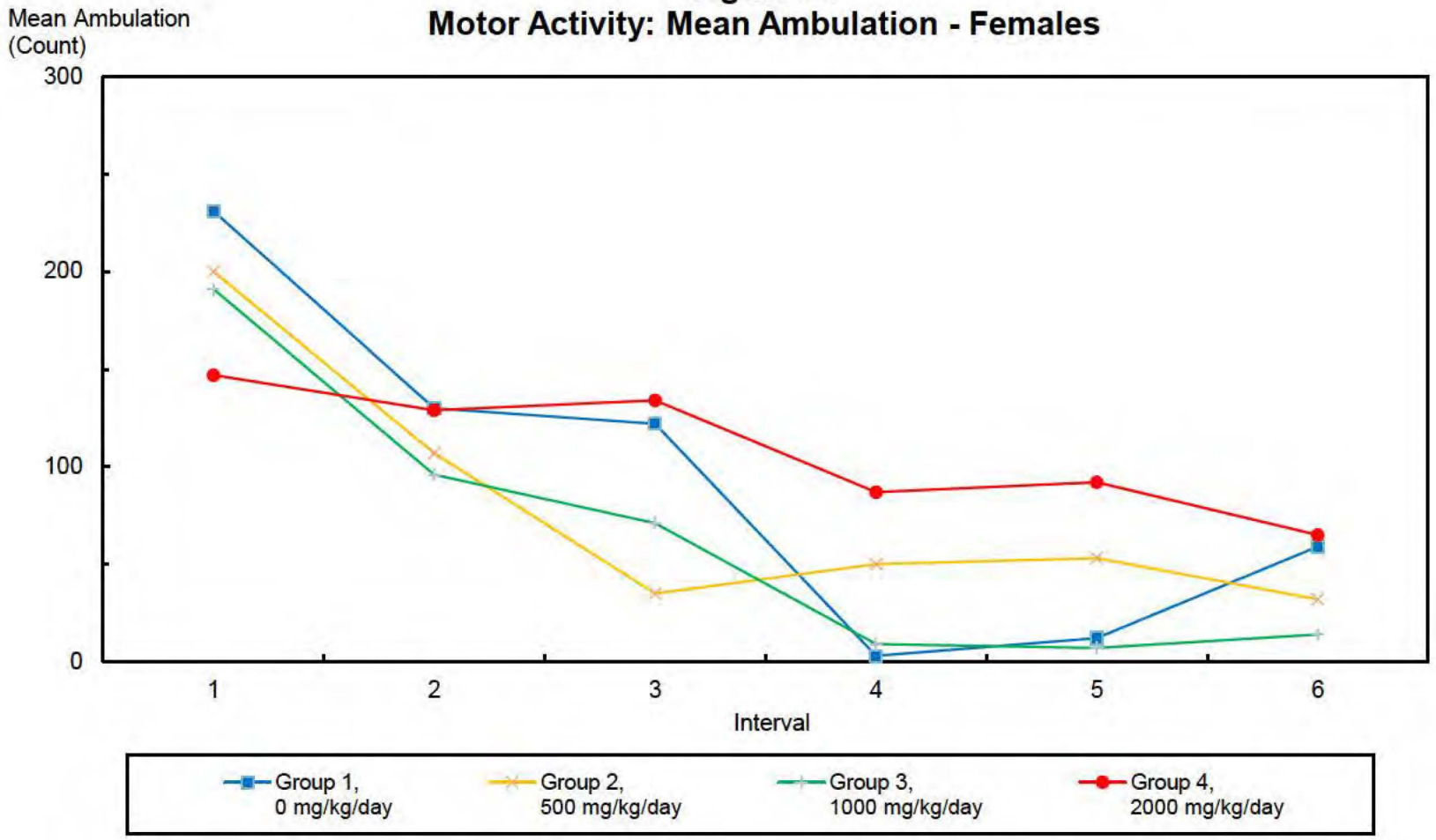
Figure 3c
Motor Activity: Mean Ambulation - Males



Figures 3

(b) (4)

Figure 3d
Motor Activity: Mean Ambulation - Females

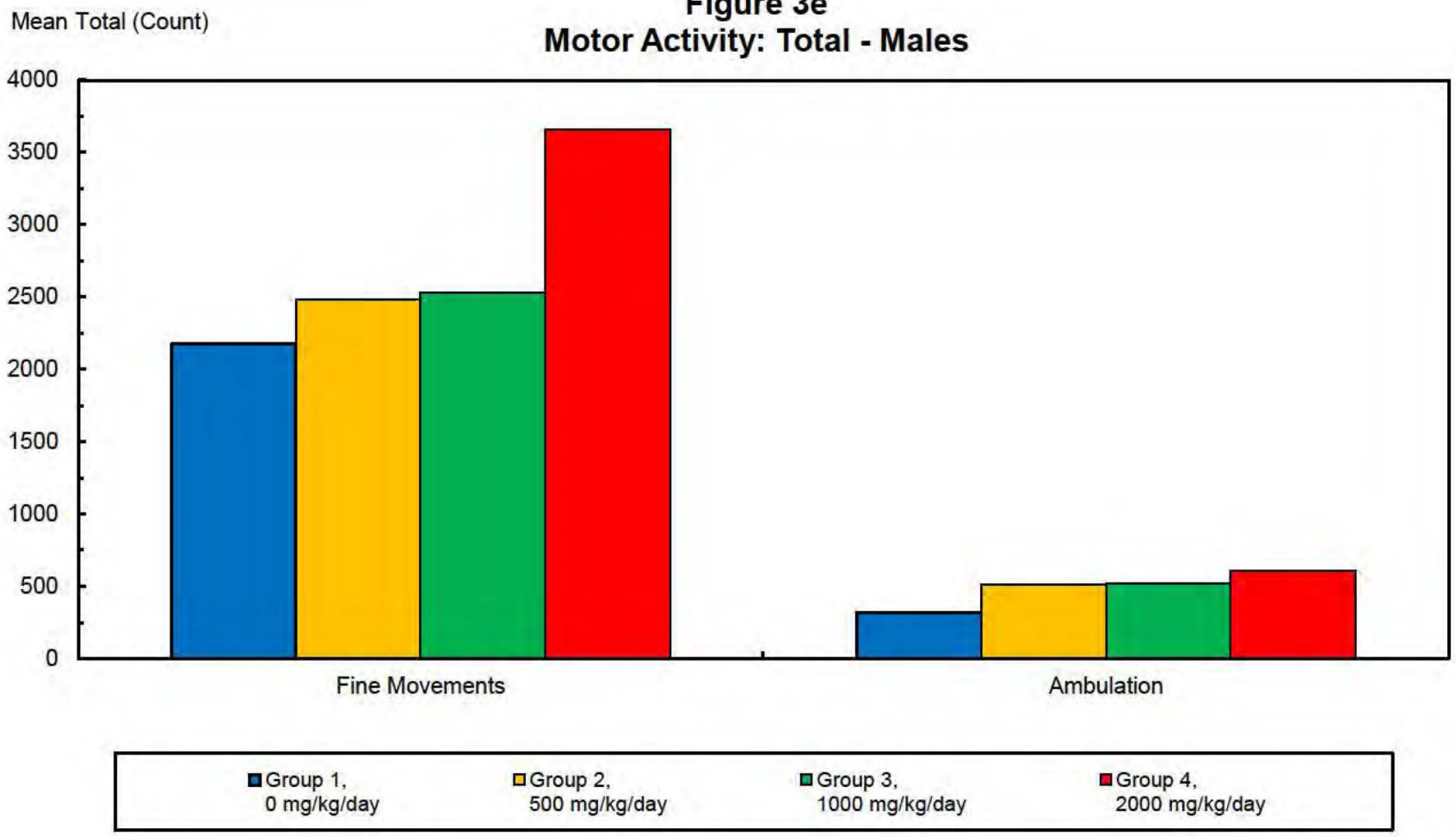


Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Figures 3

(b) (4)

Figure 3e
Motor Activity: Total - Males

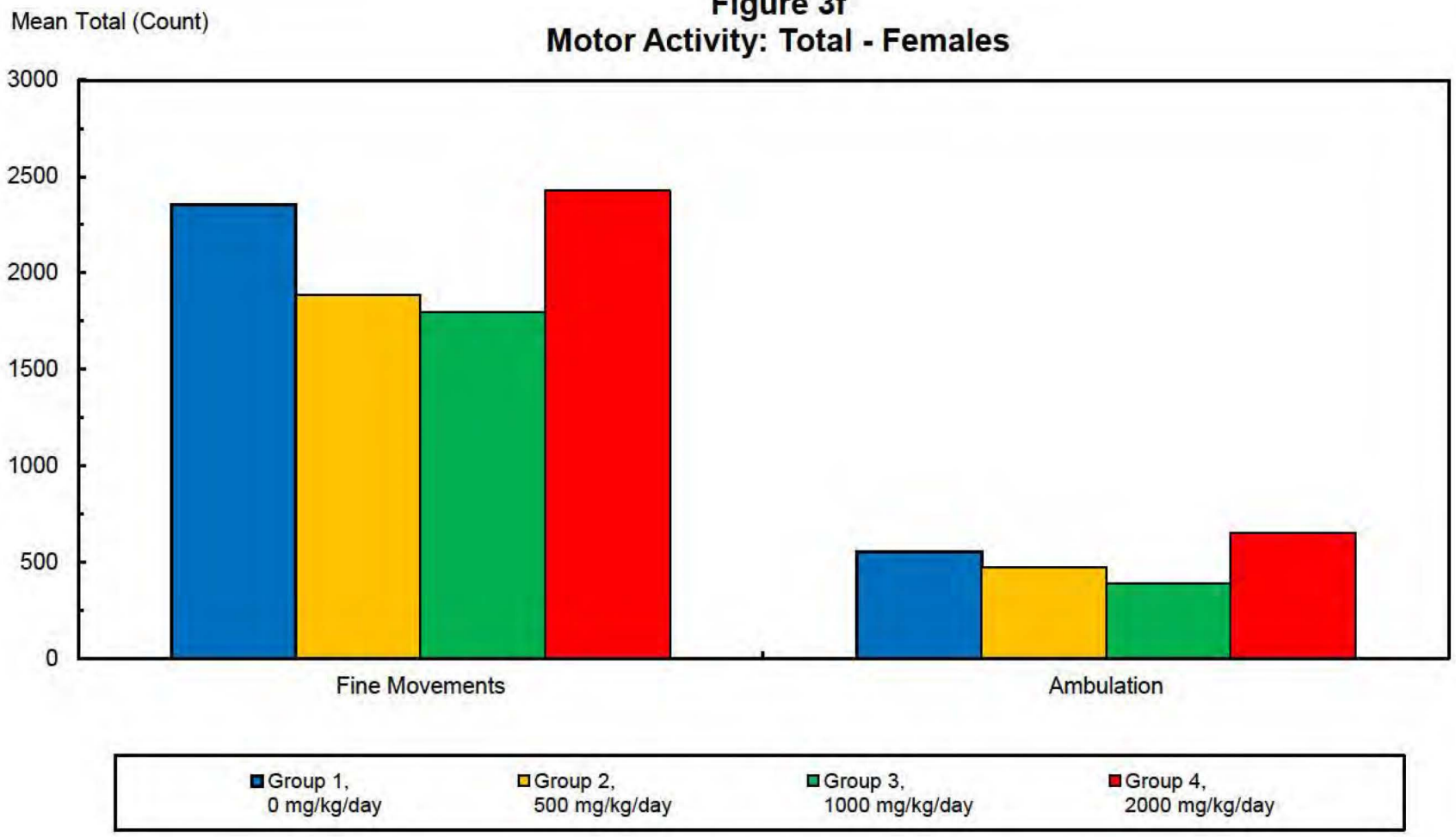


Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Figures 3

(b) (4)

Figure 3f
Motor Activity: Total - Females



SUMMARY DATA EXPLANATION PAGE

All day(s) referenced throughout the outputs generated are study days beginning with Study Day 1, the first day of dosing.

Abbreviations consistent throughout the Summary Tables.

Note: all of the abbreviations listed on these pages may not be applicable to this report.

Statistical significances arise from automatic comparisons with the principal control.

Principal control group: 1

*: 5% significance level

**: 1% significance level

***: 0.1% significance level

GENERAL

Abbreviation	Description	Abbreviation	Description
% Diff	% Difference from control group	SD	Standard deviation
Mean	Arithmetic mean	tCtrl	Mean treated group versus control group
N	Number of values included in analysis		

CLINICAL OBSERVATIONS

Abbreviation	Description	Abbreviation	Description
PT	Permanent	VET	Veterinary observation
SIRT	Sign of ill-health reaction to treatment		

Notes:
- Salivation and associated clinical observations (i.e., pedaling and/or ploughing) are presented in a specific table.
- “Other (see comment)” refers to the injury recorded for Male No. 1015 (0 mg/kg/day) on Day 26.

ARENA OBSERVATIONS

Notes:
- See Individual Data Explanation Page for specific clinical signs observed.
- No findings were observed throughout the study, therefore no data have been tabulated.

BODY WEIGHTS/BODY WEIGHT GAINS

Note:
Terminal body weights (i.e., on Day 91/92 and Day 120) are neither presented in the figures nor in body weight and body weight gain tables due to the fasting conditions.

FOOD CONSUMPTION

Abbreviation	Description
Cons	Consumption

NEUROBEHAVIORAL ASSESSMENT

Abbreviation	Description	Abbreviation	Description
oC	Celsius degree	OF	Open field
HC	Home cage	Pre	Predose
N+ve	Number positive	Resp	Response

Notes:

- During the test, rearings are expressed in counts and grip strength is expressed in grams.
- No observation was performed at the end of the recovery period since no findings were reported during the dosing period.

MOTOR ACTIVITY

Note:

No observation was performed at the end of the recovery period since no findings were reported during the dosing period.

CLINICAL PATHOLOGY

Note:

At the end of the dosing period, main animals were sampled for hematology, clinical chemistry and urinalysis on Day 91 or Day 92. For comparison and statistical analysis purposes, results are presented under the same day i.e., Day 91.

HEMATOLOGY AND COAGULATION VALUES

Abbreviation	Description	Abbreviation	Description
^x/L	10^x/L	MCV	Mean corpuscular volume
APTT	Activated partial thromboplastin time	MONO	Monocytes
BASO	Basophils	MPV	Mean platelet volume
EOS	Eosinophils	NEUT	Neutrophils
FIB	Fibrinogen concentration	PLT	Platelets
HCT	Hematocrit	PT	Prothrombin time
HGB	Hemoglobin	RBC	Red blood cells
LUC	Large unstained cells	RDWG	Red blood cell distribution width gated
LYMPH	Lymphocytes	RETIC	Reticulocytes
MCH	Mean corpuscular hemoglobin	WBC	White blood cells
MCHC	Mean corpuscular hemoglobin concentration		

CLINICAL CHEMISTRY VALUES

Abbreviation	Description	Abbreviation	Description
A/G	Albumin/Globulin	GLUC	Glucose
ALB	Albumin	HDL	High density lipoprotein
ALP	Alkaline phosphatase	K	Potassium
ALT	Alanine aminotransferase	LDL	Low density lipoprotein
AST	Aspartate aminotransferase	NA	Sodium
BILEAC	Bile acids	PHOS	Phosphorus
CA	Calcium	TBIL	Total bilirubin
CHOL	Cholesterol	TPROT	Total protein
CL	Chloride	TRIG	Triglycerides
CREAT	Creatinine	UREA	Urea nitrogen
GGT	Gamma glutamyltransferase	umol	Micromol
GLOB	Globulin		

URINE VALUES

Abbreviation	Description	Abbreviation	Description
mOsm/kg	mOsmol/kg	SPECIFIC GRAVITY	Urine specific gravity
OSMLTY	Urine osmolality	VOLUME	Urine volume

SPERM COUNT AND MOTILITY

Notes:

- At the end of the dosing period, main males were euthanized on Day 91 or Day 92. For comparison and statistical analysis purposes, results are presented together.
- Male No. 4001 (2000 mg/kg/day) showed atypical results due to unilateral diffuse atrophy not considered to be related to the administration of the test item. Data from this animal were therefore excluded from the calculation of mean and standard deviation, and consequently not taken into account in the statistical analysis.

SPERM MORPHOLOGY

Abbreviation	Description
Abnormal Sperm Combo	Abnormal sperm combined

Notes:

- At the end of the dosing period, main males were euthanized on Day 91 or Day 92. For comparison and statistical analysis purposes, results are presented under the same day i.e., Day 91.
- Male No. 4001 (2000 mg/kg/day) showed atypical results due to unilateral diffuse atrophy not considered to be related to the administration of the test item. Data from this animal were therefore excluded from the calculation of mean and standard deviation, and consequently not taken into account in the statistical analysis.

ORGAN WEIGHTS

Abbreviation	Description	Abbreviation	Description
%br	Relative to brain weight	Lt	Left
%bw	Relative to body weight	Rt	Right
Coagulating	Coagulating gland	Wt	Weight

Note:

At the end of the dosing period, main animals were euthanized on Day 91 or Day 92 (the first 5/group/sex on Day 91, the last 5/group/sex on Day 92). For comparison and statistical analysis purposes, results are presented under the same occasion (Day 91/92).

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

MACROSCOPIC/MICROSCOPIC OBSERVATIONS

Abbreviation	Description	Abbreviation	Description
?	Questionable	H	Histopathology
C	Clinical observation	M	Mass
E	Excluded	MPF	Major pathological finding
G	Gross pathology	NBF	Neutral buffered formalin
GALT	Gut-associated lymphoid tissue	TGL	Trackable gross lesion

Note:

Number of animals with necropsy/microscopic findings by organ/group/sex are presented.

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 1

16-Mar-2023 09:33:00

Summary of Clinical Observations

(b) (4)

Observation Type: Toxicology Observations From Day -8 (Start Date) to 120 (Start Date)	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Normal								
Number of Animals Affected	15	10	10	15	15	10	10	15
Number of Times Recorded	241	131	146	237	238	148	150	226
% of Affected Animals	100	100	100	100	100	100	100	100
First to Last seen	-7 119	-7 90	-7 90	-7 119	-7 119	-7 90	-7 90	-7 119
Tail, Bent (PT)								
Number of Animals Affected	0	0	1	0	0	0	0	0
Number of Times Recorded	0	0	4	0	0	0	0	0
% of Affected Animals	0	0	10	0	0	0	0	0
First to Last seen	-	-	71 90	-	-	-	-	-
Fur, Staining, Dorsal Cervical								
Number of Animals Affected	0	0	0	0	0	2	0	0
Number of Times Recorded	0	0	0	0	0	2	0	0
% of Affected Animals	0	0	0	0	0	20	0	0
First to Last seen	-	-	-	-	-	78 78	-	-
Fur, Staining, Dorsal Thoracic								
Number of Animals Affected	0	2	0	0	0	0	0	0
Number of Times Recorded	0	11	0	0	0	0	0	0
% of Affected Animals	0	20	0	0	0	0	0	0
First to Last seen	-	36 84	-	-	-	-	-	-
Fur, Thin Cover, Abdominal								
Number of Animals Affected	0	1	0	2	0	0	0	0
Number of Times Recorded	0	4	0	4	0	0	0	0
% of Affected Animals	0	10	0	13	0	0	0	0
First to Last seen	-	71 90	-	78 90	-	-	-	-

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 1

16-Mar-2023 09:33:00

Summary of Clinical Observations

(b) (4)

Observation Type: Toxicology Observations From Day -8 (Start Date) to 120 (Start Date)	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Fur, Thin Cover, Dorsal Cervical								
Number of Animals Affected	0	0	0	0	0	0	0	2
Number of Times Recorded	0	0	0	0	0	0	0	12
% of Affected Animals	0	0	0	0	0	0	0	13
First to Last seen	-	-	-	-	-	-	-	84 119
Fur, Thin Cover, Dorsal Thoracic								
Number of Animals Affected	0	0	0	1	0	0	0	1
Number of Times Recorded	0	0	0	4	0	0	0	6
% of Affected Animals	0	0	0	7	0	0	0	7
First to Last seen	-	-	-	71 90	-	-	-	84 119
Fur, Thin Cover, Face								
Number of Animals Affected	0	0	0	0	2	0	0	0
Number of Times Recorded	0	0	0	0	4	0	0	0
% of Affected Animals	0	0	0	0	13	0	0	0
First to Last seen	-	-	-	-	98 105	-	-	-
Fur, Thin Cover, Forepaw, Left								
Number of Animals Affected	0	0	0	0	0	0	0	2
Number of Times Recorded	0	0	0	0	0	0	0	3
% of Affected Animals	0	0	0	0	0	0	0	13
First to Last seen	-	-	-	-	-	-	-	78 90
Fur, Thin Cover, Forepaw, Right								
Number of Animals Affected	0	0	0	0	0	0	0	2
Number of Times Recorded	0	0	0	0	0	0	0	3
% of Affected Animals	0	0	0	0	0	0	0	13
First to Last seen	-	-	-	-	-	-	-	78 90

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 1

16-Mar-2023 09:33:00

Summary of Clinical Observations

(b) (4)

Observation Type: Toxicology Observations From Day -8 (Start Date) to 120 (Start Date)	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Fur, Thin Cover, Lumbar								
Number of Animals Affected	0	0	0	0	1	0	0	1
Number of Times Recorded	0	0	0	0	1	0	0	4
% of Affected Animals	0	0	0	0	7	0	0	7
First to Last seen	-	-	-	-	8 - 8	-	-	57 78
Skin, Scab, Dorsal Cervical								
Number of Animals Affected	1	0	0	0	0	0	0	0
Number of Times Recorded	2	0	0	0	0	0	0	0
% of Affected Animals	7	0	0	0	0	0	0	0
First to Last seen	29 36	-	-	-	-	-	-	-
Skin, Scab, Dorsal Thoracic								
Number of Animals Affected	0	2	0	0	0	0	0	0
Number of Times Recorded	0	15	0	0	0	0	0	0
% of Affected Animals	0	20	0	0	0	0	0	0
First to Last seen	-	8 84	-	-	-	-	-	-
Skin, Scab, Face								
Number of Animals Affected	0	0	0	0	1	0	0	0
Number of Times Recorded	0	0	0	0	1	0	0	0
% of Affected Animals	0	0	0	0	7	0	0	0
First to Last seen	-	-	-	-	98 98	-	-	-
Skin, Scab, Lumbar								
Number of Animals Affected	0	0	0	0	1	0	0	0
Number of Times Recorded	0	0	0	0	2	0	0	0
% of Affected Animals	0	0	0	0	7	0	0	0
First to Last seen	-	-	-	-	-7 - 1	-	-	-

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 1

16-Mar-2023 09:33:00

Summary of Clinical Observations

(b) (4)

Observation Type: Toxicology Observations From Day -8 (Start Date) to 120 (Start Date)	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Teeth, Broken								
Number of Animals Affected	1	0	0	0	0	0	0	0
Number of Times Recorded	2	0	0	0	0	0	0	0
% of Affected Animals	7	0	0	0	0	0	0	0
First to Last seen	64 71	-	-	-	-	-	-	-
Other (see comment), Forepaw, Right								
Number of Animals Affected	1	0	0	0	0	0	0	0
Number of Times Recorded	1	0	0	0	0	0	0	0
% of Affected Animals	7	0	0	0	0	0	0	0
First to Last seen	26 26	-	-	-	-	-	-	-

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 1

16-Mar-2023 09:33:00

Summary of Clinical Observations

(b) (4)

Observation Type: SIRT/Cage Side Observations From Day -8 (Start Date) to 120 (Start Date)	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Normal								
Number of Animals Affected	15	10	10	15	15	10	10	15
Number of Times Recorded	3019	1906	1892	2984	3025	1897	1891	2981
% of Affected Animals	100	100	100	100	100	100	100	100
First to Last seen	-7 120	-7 92	-7 92	-7 120	-7 120	-7 92	-7 92	-7 120
Skin, Discolored, Periorbital, Left								
Number of Animals Affected	1	0	0	0	0	0	0	0
Number of Times Recorded	2	0	0	0	0	0	0	0
% of Affected Animals	7	0	0	0	0	0	0	0
First to Last seen	70 71	-	-	-	-	-	-	-
Discharge, Color, Eye, Left								
Number of Animals Affected	1	0	0	0	0	0	0	0
Number of Times Recorded	4	0	0	0	0	0	0	0
% of Affected Animals	7	0	0	0	0	0	0	0
First to Last seen	85 87	-	-	-	-	-	-	-

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 1

16-Mar-2023 09:33:00

Summary of Clinical Observations

(b) (4)

Observation Type: Veterinary Observation From Day -8 (Start Date) to 120 (Start Date)	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Normal								
Number of Animals Affected	1	0	0	0	0	0	0	0
Number of Times Recorded	1	0	0	0	0	0	0	0
% of Affected Animals	7	0	0	0	0	0	0	0
First to Last seen	43 43	-	-	-	-	-	-	-
Skin Lesion (VET), Forelimb, Right								
Number of Animals Affected	1	0	0	0	0	0	0	0
Number of Times Recorded	4	0	0	0	0	0	0	0
% of Affected Animals	7	0	0	0	0	0	0	0
First to Last seen	28 35	-	-	-	-	-	-	-
Skin, Scab, Forelimb, Right								
Number of Animals Affected	1	0	0	0	0	0	0	0
Number of Times Recorded	1	0	0	0	0	0	0	0
% of Affected Animals	7	0	0	0	0	0	0	0
First to Last seen	39 39	-	-	-	-	-	-	-

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 2

24-Feb-2023 08:47:59

Summary of Salivation and Associated Clinical Observations

(b) (4)

Observation Type: SIRT/Cage Side Observations	Male				Female			
From Day -8 (Start Date) to 120 (Start Date)	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Normal								
Number of Animals Affected	15	10	10	15	15	10	10	15
Number of Times Recorded	3019	1906	1892	2984	3025	1897	1891	2981
% of Affected Animals	100	100	100	100	100	100	100	100
First to Last seen	-7 120	-7 92	-7 92	-7 120	-7 120	-7 92	-7 92	-7 120
Salivation								
Number of Animals Affected	0	9	10	15	0	10	10	15
Number of Times Recorded	0	14	29	55	0	24	34	62
% of Affected Animals	0	90	100	100	0	100	100	100
First to Last seen	-	24 73	24 73	17 73	-	24 73	17 73	17 73
Pedaling								
Number of Animals Affected	0	4	6	14	0	9	9	14
Number of Times Recorded	0	4	8	34	0	12	13	27
% of Affected Animals	0	40	60	93	0	90	90	93
First to Last seen	-	45 73	45 73	17 73	-	45 73	45 73	17 73
Ploughing								
Number of Animals Affected	0	6	7	14	0	6	10	15
Number of Times Recorded	0	7	10	39	0	10	17	39
% of Affected Animals	0	60	70	93	0	60	100	100
First to Last seen	-	45 73	45 73	17 73	-	45 73	17 73	17 73

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 3

16-Mar-2023 08:48:24

Summary of Body Weights

(b) (4)

Bodyweight (g)

Sex: Male		Day(s) Relative to Start Date						
		-7	1	8	16	22	29	36
0	Mean	142.8	189.9	232.8	273.2	303.7	327.8	350.7
mg/kg	SD	10.2	11.4	14.6	15.9	18.3	20.1	21.2
/day	N	15	15	15	15	15	15	15
Group 1		-	-	-	-	-	-	-
500	Mean	134.4	179.7	222.8	264.9	290.3	313.8	334.6
mg/kg	SD	10.5	10.3	11.5	8.7	10.2	11.9	15.3
/day	N	10	10	10	10	10	10	10
Group 2	%Diff	-5.9	-5.4	-4.3	-3.0	-4.4	-4.3	-4.6
1000	Mean	136.3	184.0	226.0	268.5	292.1	309.1	325.0*
mg/kg	SD	14.1	12.6	12.0	13.7	16.2	21.7	24.2
/day	N	10	10	10	10	10	10	10
Group 3	%Diff	-4.6	-3.1	-2.9	-1.7	-3.8	-5.7	-7.3
2000	Mean	135.7	185.7	225.6	266.3	294.0	317.0	333.6
mg/kg	SD	11.9	14.2	15.7	19.9	21.1	22.8	25.6
/day	N	15	15	15	15	15	15	15
Group 4	%Diff	-5.0	-2.2	-3.1	-2.5	-3.2	-3.3	-4.9

Anova & Dunnett: * =$p \leq 0.05$

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 3

16-Mar-2023 08:48:24

Summary of Body Weights

(b) (4)

Bodyweight (g)

Sex: Male		Day(s) Relative to Start Date						
		43	50	57	64	71	78	84
0	Mean	366.7	381.2	394.1	404.1	415.4	424.4	433.2
mg/kg	SD	22.2	23.5	23.9	24.4	24.5	26.1	25.9
/day	N	15	15	15	15	15	15	15
Group 1		-	-	-	-	-	-	-
500	Mean	352.5	368.7	378.3	394.5	403.3	409.5	418.5
mg/kg	SD	19.0	17.3	20.8	21.2	22.8	22.4	22.5
/day	N	10	10	10	10	10	10	10
Group 2	%Diff	-3.9	-3.3	-4.0	-2.4	-2.9	-3.5	-3.4
1000	Mean	339.4*	352.0*	364.2	377.1	385.9	391.2	399.8
mg/kg	SD	27.5	27.6	30.5	30.9	32.7	33.8	33.4
/day	N	10	10	10	10	10	10	10
Group 3	%Diff	-7.5	-7.7	-7.6	-6.7	-7.1	-7.8	-7.7
2000	Mean	349.5	363.9	375.2	390.7	399.7	405.5	414.0
mg/kg	SD	26.1	29.1	29.4	32.3	32.4	33.9	33.8
/day	N	15	15	15	15	15	15	15
Group 4	%Diff	-4.7	-4.5	-4.8	-3.3	-3.8	-4.5	-4.4

Anova & Dunnett: * =$p \leq 0.05$

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 3

16-Mar-2023 08:48:24

Summary of Body Weights

(b) (4)

Bodyweight (g)

Sex: Male		Day(s) Relative to Start Date				
		90	98	105	112	119
0	Mean	439.6	440.4	441.4	443.4	451.8
mg/kg	SD	26.3	20.5	20.8	21.3	23.5
/day	N	15	5	5	5	5
Group 1		-	-	-	-	-
500	Mean	424.9	-	-	-	-
mg/kg	SD	23.6	-	-	-	-
/day	N	10	-	-	-	-
Group 2	%Diff	-3.3	-	-	-	-
1000	Mean	405.5*	-	-	-	-
mg/kg	SD	34.1	-	-	-	-
/day	N	10	-	-	-	-
Group 3	%Diff	-7.8	-	-	-	-
2000	Mean	418.1	419.0	418.8	422.0	425.8
mg/kg	SD	32.9	24.2	24.0	25.6	27.9
/day	N	15	5	5	5	5
Group 4	%Diff	-4.9	-4.9	-5.1	-4.8	-5.8

Anova & Dunnett: * =$p \leq 0.05$

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 3

16-Mar-2023 08:48:24

Summary of Body Weights

(b) (4)

Bodyweight (g)

Sex: Female		Day(s) Relative to Start Date						
		-7	1	8	16	22	29	36
0	Mean	127.4	153.5	168.8	190.3	200.3	213.2	225.0
mg/kg	SD	8.6	10.3	14.0	14.2	13.6	15.8	20.4
/day	N	15	15	15	15	15	15	15
Group 1		-	-	-	-	-	-	-
500	Mean	127.0	150.3	169.1	192.7	206.5	216.7	227.2
mg/kg	SD	6.9	6.3	6.5	8.7	11.1	12.2	13.6
/day	N	10	10	10	10	10	10	10
Group 2	%Diff	-0.3	-2.1	0.2	1.3	3.1	1.6	1.0
1000	Mean	131.3	155.7	177.0	200.7	211.6	224.2	237.3
mg/kg	SD	8.8	9.7	10.2	9.8	10.2	13.3	14.3
/day	N	10	10	10	10	10	10	10
Group 3	%Diff	3.1	1.5	4.9	5.5	5.7	5.2	5.5
2000	Mean	129.7	154.6	176.5	199.3	212.3	226.4	234.9
mg/kg	SD	7.4	10.6	13.3	15.0	14.6	17.1	18.5
/day	N	15	15	15	15	15	15	15
Group 4	%Diff	1.8	0.7	4.5	4.7	6.0	6.2	4.4

Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 3

16-Mar-2023 08:48:24

Summary of Body Weights

(b) (4)

Bodyweight (g)

Sex: Female		Day(s) Relative to Start Date						
		43	50	57	64	71	78	84
0	Mean	232.6	238.7	243.5	249.9	255.5	256.5	262.4
mg/kg	SD	20.2	18.6	17.9	21.7	24.4	20.9	24.4
/day	N	15	15	15	15	15	15	15
Group 1		-	-	-	-	-	-	-
500	Mean	236.4	244.7	246.6	252.5	256.1	260.5	265.3
mg/kg	SD	11.8	14.6	14.4	15.3	12.4	15.6	15.9
/day	N	10	10	10	10	10	10	10
Group 2	%Diff	1.6	2.5	1.3	1.1	0.2	1.6	1.1
1000	Mean	246.3	255.2	256.8	267.0	269.7	271.2	275.8
mg/kg	SD	15.7	15.6	15.1	14.2	17.4	16.4	16.7
/day	N	10	10	10	10	10	10	10
Group 3	%Diff	5.9	6.9	5.5	6.9	5.6	5.7	5.1
2000	Mean	247.1	252.7	255.6	262.4	269.0	269.0	271.7
mg/kg	SD	16.9	17.2	18.4	19.2	17.0	17.9	19.9
/day	N	15	15	15	15	15	15	15
Group 4	%Diff	6.2	5.9	5.0	5.0	5.3	4.9	3.5

Anova & Dunnett

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 3

16-Mar-2023 08:48:24

Summary of Body Weights

(b) (4)

Bodyweight (g)

Sex: Female		Day(s) Relative to Start Date				
		90 [G]	98 [G1]	105 [G1]	112 [G]	119 [G]
0	Mean	263.9	277.4	276.6	278.4	279.2
mg/kg	SD	26.2	17.6	20.2	24.2	19.5
/day	N	15	5	5	5	5
Group 1		-	-	-	-	-
500	Mean	266.3	-	-	-	-
mg/kg	SD	15.9	-	-	-	-
/day	N	10	-	-	-	-
Group 2	%Diff	0.9	-	-	-	-
1000	Mean	276.4	-	-	-	-
mg/kg	SD	17.5	-	-	-	-
/day	N	10	-	-	-	-
Group 3	%Diff	4.7	-	-	-	-
2000	Mean	273.9	271.0	269.4	269.4	271.6
mg/kg	SD	18.7	7.2	12.0	13.3	11.8
/day	N	15	5	5	5	5
Group 4	%Diff	3.8	-2.3	-2.6	-3.2	-2.7

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 4

24-Feb-2023 08:45:10

Summary of Body Weight Gains (g)

(b) (4)

Bodyweight Gain (Interval)

Sex: Male		Day(s) Relative to Start Date						
		-7 → 1 [G]	1 → 8 [G1]	8 → 16 [G1]	16 → 22 [G]	22 → 29 [G1]	29 → 36 [G]	36 → 43 [G1]
0	Mean	47.1	42.9	40.4	30.5	24.1	22.9	16.0
mg/kg	SD	4.8	5.0	4.3	4.1	4.1	3.4	3.8
/day	N	15	15	15	15	15	15	15
Group 1		-	-	-	-	-	-	-
500	Mean	45.3	43.1	42.1	25.4	23.5	20.8	17.9
mg/kg	SD	1.7	3.5	6.9	4.2	5.3	5.9	5.9
/day	N	10	10	10	10	10	10	10
Group 2		-	-	-	-	-	-	-
1000	Mean	47.7	42.0	42.5	23.6*	17.0*	15.9**	14.4
mg/kg	SD	4.4	4.8	5.6	7.0	7.8	4.1	6.8
/day	N	10	10	10	10	10	10	10
Group 3		-	-	-	-	-	-	-
2000	Mean	50.0	39.9	40.7	27.7	23.0	16.6*	15.9
mg/kg	SD	3.5	4.2	11.4	8.5	6.7	6.6	6.0
/day	N	15	15	15	15	15	15	15
Group 4		-	-	-	-	-	-	-

[G] - Kruskal-Wallis & Dunn: * = $p \leq 0.05$; ** = $p \leq 0.01$

[G1] - Anova & Dunnett: * = $p \leq 0.05$

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 4

24-Feb-2023 08:45:10

Summary of Body Weight Gains (g)

(b) (4)

Bodyweight Gain (Interval)

Sex: Male		Day(s) Relative to Start Date						
		43 → 50	50 → 57	57 → 64	64 → 71	71 → 78	78 → 84	84 → 90
0	Mean	14.5	12.9	9.9	11.3	9.0	8.8	6.4
mg/kg	SD	4.9	4.0	4.2	2.5	3.8	3.8	3.7
/day	N	15	15	15	15	15	15	15
Group 1		-	-	-	-	-	-	-
500	Mean	16.2	9.6	16.2**	8.8	6.2	9.0	6.4
mg/kg	SD	3.9	4.5	3.2	4.4	4.5	4.4	2.6
/day	N	10	10	10	10	10	10	10
Group 2		-	-	-	-	-	-	-
1000	Mean	12.6	12.2	12.9	8.8	5.3*	8.6	5.7
mg/kg	SD	3.7	4.3	4.1	2.7	3.7	3.7	3.9
/day	N	10	10	10	10	10	10	10
Group 3		-	-	-	-	-	-	-
2000	Mean	14.5	11.3	15.5**	8.9	5.8	8.5	4.1
mg/kg	SD	5.4	4.8	4.5	4.5	2.7	4.0	4.2
/day	N	15	15	15	15	15	15	15
Group 4		-	-	-	-	-	-	-

Anova & Dunnett: * $p \leq 0.05$; ** $p \leq 0.01$

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 4

24-Feb-2023 08:45:10

Summary of Body Weight Gains (g)

(b) (4)

Bodyweight Gain (Interval)

Sex: Male		Day(s) Relative to Start Date					
		1 → 90 [G]	90 → 98 [G1]	98 → 105 [G]	105 → 112 [G]	112 → 119 [G]	90 → 119 [G]
0	Mean	249.7	6.0	1.0	2.0	8.4	17.4
mg/kg	SD	20.9	1.9	2.2	6.3	7.2	3.8
/day	N	15	5	5	5	5	5
Group 1		-	-	-	-	-	-
500	Mean	245.2	-	-	-	-	-
mg/kg	SD	29.9	-	-	-	-	-
/day	N	10	-	-	-	-	-
Group 2		-	-	-	-	-	-
1000	Mean	221.5	-	-	-	-	-
mg/kg	SD	34.8	-	-	-	-	-
/day	N	10	-	-	-	-	-
Group 3		-	-	-	-	-	-
2000	Mean	232.5	3.0	-0.2	3.2	3.8	9.8
mg/kg	SD	29.5	5.2	4.4	2.5	3.5	8.8
/day	N	15	5	5	5	5	5
Group 4		-	-	-	-	-	-

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 4

24-Feb-2023 08:45:10

Summary of Body Weight Gains (g)

(b) (4)

Bodyweight Gain (Interval)

Sex: Female		Day(s) Relative to Start Date						
		-7 → 1	1 → 8	8 → 16	16 → 22	22 → 29	29 → 36	36 → 43
0	Mean	26.1	15.3	21.5	10.0	12.9	11.8	7.6
mg/kg	SD	5.6	8.1	4.6	6.3	7.2	8.8	7.1
/day	N	15	15	15	15	15	15	15
Group 1		-	-	-	-	-	-	-
500	Mean	23.3	18.8	23.6	13.8	10.2	10.5	9.2
mg/kg	SD	6.2	6.4	3.9	5.1	4.7	6.6	5.7
/day	N	10	10	10	10	10	10	10
Group 2		-	-	-	-	-	-	-
1000	Mean	24.4	21.3	23.7	10.9	12.6	13.1	9.0
mg/kg	SD	5.0	6.3	4.1	5.4	5.4	8.4	5.7
/day	N	10	10	10	10	10	10	10
Group 3		-	-	-	-	-	-	-
2000	Mean	24.9	21.9	22.8	13.0	14.1	8.5	12.2
mg/kg	SD	5.3	5.9	4.4	5.6	7.4	6.5	4.9
/day	N	15	15	15	15	15	15	15
Group 4		-	-	-	-	-	-	-

Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 4

24-Feb-2023 08:45:10

Summary of Body Weight Gains (g)

(b) (4)

Bodyweight Gain (Interval)

Sex: Female		Day(s) Relative to Start Date						
		43 → 50 [G]	50 → 57 [G1]	57 → 64 [G1]	64 → 71 [G1]	71 → 78 [G1]	78 → 84 [G1]	84 → 90 [G1]
0	Mean	6.1	4.8	6.4	5.6	1.0	5.9	1.5
mg/kg	SD	5.3	6.3	6.5	8.9	6.8	6.5	9.8
/day	N	15	15	15	15	15	15	15
Group 1		-	-	-	-	-	-	-
500	Mean	8.3	1.9	5.9	3.6	4.4	4.8	1.0
mg/kg	SD	6.4	5.5	5.5	8.6	8.2	5.8	4.0
/day	N	10	10	10	10	10	10	10
Group 2		-	-	-	-	-	-	-
1000	Mean	8.9	1.6	10.2	2.7	1.5	4.6	0.6
mg/kg	SD	10.0	11.9	5.5	6.0	6.0	6.3	5.0
/day	N	10	10	10	10	10	10	10
Group 3		-	-	-	-	-	-	-
2000	Mean	5.6	2.9	6.8	6.6	0.0	2.7	2.2
mg/kg	SD	4.5	5.3	6.1	4.5	3.9	6.5	6.2
/day	N	15	15	15	15	15	15	15
Group 4		-	-	-	-	-	-	-

[G] -Kruskal-Wallis & Dunn

[G1] -Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 4

24-Feb-2023 08:45:10

Summary of Body Weight Gains (g)

(b) (4)

Bodyweight Gain (Interval)

Sex: Female		Day(s) Relative to Start Date					
		1 → 90	90 → 98	98 → 105	105 → 112	112 → 119	90 → 119
0	Mean	110.5	-1.2	-0.8	1.8	0.8	0.6
mg/kg	SD	21.2	13.2	3.7	5.0	6.0	9.9
/day	N	15	5	5	5	5	5
Group 1		-	-	-	-	-	-
500	Mean	116.0	-	-	-	-	-
mg/kg	SD	12.8	-	-	-	-	-
/day	N	10	-	-	-	-	-
Group 2		-	-	-	-	-	-
1000	Mean	120.7	-	-	-	-	-
mg/kg	SD	17.8	-	-	-	-	-
/day	N	10	-	-	-	-	-
Group 3		-	-	-	-	-	-
2000	Mean	119.3	-2.4	-1.6	0.0	2.2	-1.8
mg/kg	SD	13.1	4.0	7.4	4.4	4.1	7.0
/day	N	15	5	5	5	5	5
Group 4		-	-	-	-	-	-

Anova & Dunnett

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 5

24-Feb-2023 08:45:04

Summary of Food Consumption

(b) (4)

Daily Food Cons Per Animal (g)

Sex: Male		Day(s) Relative to Animal Start Date						
		1 → 8	8 → 16	16 → 22	22 → 29	29 → 36	36 → 43	43 → 50
0	Mean	23.1	25.9	27.4	26.9	27.1	26.4	25.8
mg/kg	SD	0.4	0.5	0.9	1.0	0.8	1.1	1.4
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
500	Mean	23.0	26.1	26.9	25.8	26.8	26.1	24.2
mg/kg	SD	0.5	0.5	0.7	1.3	1.7	1.5	2.3
/day	N	3	3	3	3	3	3	3
Group 2	%Diff	-0.5	0.8	-1.7	-4.3	-1.1	-1.2	-6.3
1000	Mean	23.0	26.1	25.5	24.0	23.8	23.9	23.0
mg/kg	SD	1.3	1.1	2.0	2.1	1.9	1.8	4.0
/day	N	3	3	3	3	3	3	3
Group 3	%Diff	-0.7	0.7	-6.8	-10.8	-12.1	-9.6	-11.1
2000	Mean	23.4	26.8	27.4	27.0	26.7	26.1	25.0
mg/kg	SD	1.3	2.1	2.9	2.9	2.6	2.7	3.8
/day	N	5	5	5	5	5	5	5
Group 4	%Diff	1.1	3.4	-0.1	0.3	-1.4	-1.1	-3.2

Anova & Dunnett

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 5

24-Feb-2023 08:45:04

Summary of Food Consumption

(b) (4)

Daily Food Cons Per Animal (g)

Sex: Male		Day(s) Relative to Animal Start Date						
		50 → 57	57 → 64	64 → 71	71 → 78	78 → 84	84 → 90	1 → 90
0	Mean	24.4	24.8	24.4	24.9	24.6	23.5	25.3
mg/kg	SD	3.3	1.0	0.9	1.1	1.1	1.3	0.8
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
500	Mean	24.0	24.7	24.5	24.6	24.3	23.3	25.0
mg/kg	SD	1.3	1.3	1.5	1.6	1.7	1.7	1.0
/day	N	3	3	3	3	3	3	3
Group 2	%Diff	-1.5	-0.3	0.1	-1.3	-1.6	-0.9	-1.5
1000	Mean	22.9	23.1	22.5	23.0	22.4	21.9	23.5
mg/kg	SD	1.5	0.5	0.8	1.0	0.7	0.7	1.4
/day	N	3	3	3	3	3	3	3
Group 3	%Diff	-6.2	-6.5	-7.8	-7.8	-9.1	-7.0	-7.3
2000	Mean	24.4	25.1	24.6	24.9	24.8	23.1	25.4
mg/kg	SD	2.6	2.7	2.7	2.4	2.6	2.1	2.5
/day	N	5	5	5	5	5	5	5
Group 4	%Diff	0.3	1.5	0.7	-0.2	0.8	-2.0	0.1

Anova & Dunnett

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 5

24-Feb-2023 08:45:04

Summary of Food Consumption

(b) (4)

Daily Food Cons Per Animal (g)

Sex: Male		Day(s) Relative to Animal Start Date				
		90 → 98	98 → 105	105 → 112	112 → 119	90 → 119
0	Mean	25.0n	24.3n	25.0n	24.8n	24.8n
mg/kg	SD	0.9	1.0	0.8	0.1	0.7
/day	N	2	2	2	2	2
Group 1		-	-	-	-	-
500	Mean	-	-	-	-	-
mg/kg	SD	-	-	-	-	-
/day	N	-	-	-	-	-
Group 2	%Diff	-	-	-	-	-
1000	Mean	-	-	-	-	-
mg/kg	SD	-	-	-	-	-
/day	N	-	-	-	-	-
Group 3	%Diff	-	-	-	-	-
2000	Mean	24.6n	23.9n	24.0n	24.7n	24.3n
mg/kg	SD	0.2	0.1	0.8	1.0	0.4
/day	N	2	2	2	2	2
Group 4	%Diff	-1.5	-1.5	-3.7	-0.1	-1.7

n Inappropriate for statistics

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 5

24-Feb-2023 08:45:04

Summary of Food Consumption

(b) (4)

Daily Food Cons Per Animal (g)

Sex: Female		Day(s) Relative to Animal Start Date						
		1 → 8	8 → 16	16 → 22	22 → 29	29 → 36	36 → 43	43 → 50
0	Mean	16.4	18.2	18.5	18.5	19.6	19.2	18.9
mg/kg	SD	1.3	1.0	0.9	0.9	1.0	0.7	1.0
/day	N	3	3	3	3	3	3	3
Group 1		-	-	-	-	-	-	-
500	Mean	16.8n	20.4n	19.5n	18.5n	19.8n	19.8n	21.4n
mg/kg	SD	0.3	1.6	0.4	0.8	0.1	0.3	2.3
/day	N	2	2	2	2	2	2	2
Group 2	%Diff	2.0	12.1	5.4	0.4	1.4	3.1	13.2
1000	Mean	16.9n	20.2n	20.5n	19.6n	20.8n	20.8n	20.5n
mg/kg	SD	1.7	0.0	0.3	0.3	0.0	0.0	0.0
/day	N	2	2	2	2	2	2	2
Group 3	%Diff	2.6	11.5	10.5	6.2	6.3	8.1	8.5
2000	Mean	17.1	20.5*	20.5	19.8	20.6	20.7*	20.5
mg/kg	SD	0.9	0.5	1.1	1.2	0.8	0.6	1.1
/day	N	3	3	3	3	3	3	3
Group 4	%Diff	4.3	12.7	10.5	7.1	5.5	7.8	8.7

Anova & Dunnett: * = $p \leq 0.05$; n = Inappropriate for statistics

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 5

24-Feb-2023 08:45:04

Summary of Food Consumption

(b) (4)

Daily Food Cons Per Animal (g)

Sex: Female		Day(s) Relative to Animal Start Date						
		50 → 57	57 → 64	64 → 71	71 → 78	78 → 84	84 → 90	1 → 90
0	Mean	18.2	18.5	17.9	18.4	18.9	16.8	18.3
mg/kg	SD	0.5	0.6	0.5	0.5	0.7	0.3	0.8
/day	N	3	3	3	3	3	3	3
Group 1		-	-	-	-	-	-	-
500	Mean	17.7n	18.6n	18.4n	18.7n	18.7n	16.9n	18.9n
mg/kg	SD	0.6	0.8	0.1	0.2	1.0	0.4	0.5
/day	N	2	2	2	2	2	2	2
Group 2	%Diff	-2.9	0.9	3.0	1.7	-1.3	0.7	3.2
1000	Mean	19.0n	20.0n	19.2n	19.5n	20.0n	17.8n	19.6n
mg/kg	SD	0.3	0.1	0.2	0.1	0.0	0.2	0.1
/day	N	2	2	2	2	2	2	2
Group 3	%Diff	4.1	8.0	7.3	6.5	5.7	5.9	7.1
2000	Mean	19.3	20.4*	19.6*	19.5	19.9	17.9	19.7
mg/kg	SD	0.9	0.8	0.9	0.6	0.5	1.2	0.7
/day	N	3	3	3	3	3	3	3
Group 4	%Diff	5.7	10.2	9.5	6.3	5.1	6.7	7.8

Anova & Dunnett: * = $p \leq 0.05$; n = Inappropriate for statistics

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 5

24-Feb-2023 08:45:04

Summary of Food Consumption

(b) (4)

Daily Food Cons Per Animal (g)

Sex: Female		Day(s) Relative to Animal Start Date				
		90 → 98	98 → 105	105 → 112	112 → 119	90 → 119
0	Mean	18.3 n	18.3 n	18.3 n	17.7 n	18.2 n
mg/kg	SD	-	-	-	-	-
/day	N	1	1	1	1	1
Group 1		-	-	-	-	-
500	Mean	-	-	-	-	-
mg/kg	SD	-	-	-	-	-
/day	N	-	-	-	-	-
Group 2	%Diff	-	-	-	-	-
1000	Mean	-	-	-	-	-
mg/kg	SD	-	-	-	-	-
/day	N	-	-	-	-	-
Group 3	%Diff	-	-	-	-	-
2000	Mean	19.5 n	19.5 n	19.5 n	19.3 n	19.5 n
mg/kg	SD	-	-	-	-	-
/day	N	1	1	1	1	1
Group 4	%Diff	6.4	6.7	6.7	9.2	7.2

n Inappropriate for statistics

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 6

22-Feb-2023 12:02:43

Summary of Neurobehavioral Evaluation: Activity

(b) (4)

Day: 85 Relative to Start Date (Pre)

Sex: Male		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Arousal/Alertness	N	5	5	5	5
-2 Very low	N+ve	0	0	0	0
-1 Low	N+ve	0	1	0	0
0 Normal	N+ve	5	4	5	5
1 High	N+ve	0	0	0	0
2 Very High	N+ve	0	0	0	0
Posture/Body Carriage	N	5	5	5	5
-2 Prostrate or flattened	N+ve	0	0	0	0
-1 Hunched or lying low	N+ve	0	0	0	0
0 Normal (asleep/sit/stand)	N+ve	5	5	5	5
Stereotypy (Home Cage)	N	5	5	5	5
0 Not present; Normal	N+ve	5	5	5	5
1 Licking, biting, grooming	N+ve	0	0	0	0
2 Mouth movements/weaving	N+ve	0	0	0	0
3 Circling, retropulsion	N+ve	0	0	0	0
4 Self-mutilation	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 6

22-Feb-2023 12:02:43

Summary of Neurobehavioral Evaluation: Activity

(b) (4)

Day: 85 Relative to Start Date (Pre)

Sex: Male		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Stereotypy (Open Field)	N	5	5	5	5
0 Not present; Normal	N+ve	5	5	5	5
1 Licking, biting, grooming	N+ve	0	0	0	0
2 Mouth movements/weaving	N+ve	0	0	0	0
3 Circling, retropulsion	N+ve	0	0	0	0
4 Self-mutilation	N+ve	0	0	0	0
Rearing [G]	Mean	6.0	6.0	13.0	8.8
	SD	4.2	5.3	6.2	4.1
	N	5	5	5	5
	%Diff	-	0.0	116.7	46.7
Appearance	N	5	5	5	5
0 Clean and groomed	N+ve	5	5	5	5
1 Slightly unkempt	N+ve	0	0	0	0
2 Extremely unkempt	N+ve	0	0	0	0

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 6

22-Feb-2023 12:02:43

Summary of Neurobehavioral Evaluation: Activity

(b) (4)

Day: 86 Relative to Start Date (Pre)

Sex: Female		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Arousal/Alertness	N	5	5	5	5
-2 Very low	N+ve	0	0	0	0
-1 Low	N+ve	0	0	0	0
0 Normal	N+ve	5	5	5	5
1 High	N+ve	0	0	0	0
2 Very High	N+ve	0	0	0	0
Posture/Body Carriage	N	5	5	5	5
-2 Prostrate or flattened	N+ve	0	0	0	0
-1 Hunched or lying low	N+ve	0	0	0	0
0 Normal (asleep/sit/stand)	N+ve	5	5	5	5
Stereotypy (Home Cage)	N	5	5	5	5
0 Not present; Normal	N+ve	5	5	5	5
1 Licking, biting, grooming	N+ve	0	0	0	0
2 Mouth movements/weaving	N+ve	0	0	0	0
3 Circling, retropulsion	N+ve	0	0	0	0
4 Self-mutilation	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 6

22-Feb-2023 12:02:43

Summary of Neurobehavioral Evaluation: Activity

(b) (4)

Day: 86 Relative to Start Date (Pre)

Sex: Female		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Stereotypy (Open Field)	N	5	5	5	5
0 Not present; Normal	N+ve	5	5	5	5
1 Licking, biting, grooming	N+ve	0	0	0	0
2 Mouth movements/weaving	N+ve	0	0	0	0
3 Circling, retropulsion	N+ve	0	0	0	0
4 Self-mutilation	N+ve	0	0	0	0
Rearing [G]	Mean	4.8	5.6	6.0	4.0
	SD	3.9	3.6	3.3	4.2
	N	5	5	5	5
	%Diff	-	16.7	25.0	-16.7
Appearance	N	5	5	5	5
0 Clean and groomed	N+ve	5	5	5	5
1 Slightly unkempt	N+ve	0	0	0	0
2 Extremely unkempt	N+ve	0	0	0	0

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 7

22-Feb-2023 12:02:50

Summary of Neurobehavioral Evaluation: Excitability

(b) (4)

Day: 85 Relative to Start Date (Pre)

Sex: Male		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Vocalizations	N	5	5	5	5
0 Once/not at all	N+ve	5	5	5	5
1 More than once	N+ve	0	0	0	0
Startle Response	N	5	5	5	5
-1 No reaction	N+ve	0	0	0	0
0 Normal reaction	N+ve	5	5	5	5
1 Exaggerated Reaction	N+ve	0	0	0	0
Ease of Removal	N	5	5	5	5
-1 Very easy	N+ve	0	0	0	0
0 Easy	N+ve	5	5	5	5
1 Moderate	N+ve	0	0	0	0
2 Difficult	N+ve	0	0	0	0
Handling Reactivity	N	5	5	5	5
-1 Very low	N+ve	0	0	0	0
0 Low	N+ve	5	5	5	5
1 Moderate	N+ve	0	0	0	0
2 High	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 7

22-Feb-2023 12:02:50

Summary of Neurobehavioral Evaluation: Excitability

(b) (4)

Day: 85 Relative to Start Date (Pre)

Sex: Male		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Convulsions (Home Cage)	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Clonic movement	N+ve	0	0	0	0
2 Clonic tremors	N+ve	0	0	0	0
3 Severe clonus	N+ve	0	0	0	0
4 Whole body convulsions	N+ve	0	0	0	0
Convulsions (Open Field)	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Clonic movement	N+ve	0	0	0	0
2 Clonic tremors	N+ve	0	0	0	0
3 Severe clonus	N+ve	0	0	0	0
4 Whole body convulsions	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 7

22-Feb-2023 12:02:50

Summary of Neurobehavioral Evaluation: Excitability

(b) (4)

Day: 86 Relative to Start Date (Pre)

Sex: Female		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Vocalizations	N	5	5	5	5
0 Once/not at all	N+ve	5	5	5	5
1 More than once	N+ve	0	0	0	0
Startle Response	N	5	5	5	5
-1 No reaction	N+ve	0	0	0	0
0 Normal reaction	N+ve	5	5	5	5
1 Exaggerated Reaction	N+ve	0	0	0	0
Ease of Removal	N	5	5	5	5
-1 Very easy	N+ve	0	0	0	0
0 Easy	N+ve	5	5	5	5
1 Moderate	N+ve	0	0	0	0
2 Difficult	N+ve	0	0	0	0
Handling Reactivity	N	5	5	5	5
-1 Very low	N+ve	0	0	0	0
0 Low	N+ve	5	5	5	5
1 Moderate	N+ve	0	0	0	0
2 High	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 7

22-Feb-2023 12:02:50

Summary of Neurobehavioral Evaluation: Excitability

(b) (4)

Day: 86 Relative to Start Date (Pre)

Sex: Female		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Convulsions (Home Cage)	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Clonic movement	N+ve	0	0	0	0
2 Clonic tremors	N+ve	0	0	0	0
3 Severe clonus	N+ve	0	0	0	0
4 Whole body convulsions	N+ve	0	0	0	0
Convulsions (Open Field)	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Clonic movement	N+ve	0	0	0	0
2 Clonic tremors	N+ve	0	0	0	0
3 Severe clonus	N+ve	0	0	0	0
4 Whole body convulsions	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 8

22-Feb-2023 12:02:50

Summary of Neurobehavioral Evaluation: Autonomic

(b) (4)

Day: 85 Relative to Start Date (Pre)

Sex: Male		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Exophthalmus	N	5	5	5	5
0 Not present	N+ve	5	5	5	5
1 Present	N+ve	0	0	0	0
Lacrimation	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Slight	N+ve	0	0	0	0
2 Severe	N+ve	0	0	0	0
Erected Fur	N	5	5	5	5
0 Not present	N+ve	5	5	5	5
1 Present	N+ve	0	0	0	0
Pupil Response	N	5	5	5	5
0 Normal constriction	N+ve	5	5	5	5
1 Partial/no constriction	N+ve	0	0	0	0
2 Pre-existing constriction	N+ve	0	0	0	0
Salivation	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Slight	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 8

22-Feb-2023 12:02:50

Summary of Neurobehavioral Evaluation: Autonomic

(b) (4)

Day: 85 Relative to Start Date (Pre)

Sex: Male		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
2 Severe	N+ve	0	0	0	0
Defecation	N	5	5	5	5
-1 Absent	N+ve	5	4	4	4
0 Normal	N+ve	0	1	1	1
1 Abnormal	N+ve	0	0	0	0
Palpebral Closure/Ptosis (HC)	N	5	5	5	5
0 Eyelids wide open	N+ve	5	5	5	5
1 Eyelids droop halfway	N+ve	0	0	0	0
2 Eyelids completely shut	N+ve	0	0	0	0
Palpebral Closure/Ptosis (OF)	N	5	5	5	5
0 Eyelids wide open	N+ve	5	5	5	5
1 Eyelids droop halfway	N+ve	0	0	0	0
2 Eyelids completely shut	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 8

22-Feb-2023 12:02:50

Summary of Neurobehavioral Evaluation: Autonomic

(b) (4)

Day: 86 Relative to Start Date (Pre)

Sex: Female		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Exophthalmus	N	5	5	5	5
0 Not present	N+ve	5	5	5	5
1 Present	N+ve	0	0	0	0
Lacrimation	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Slight	N+ve	0	0	0	0
2 Severe	N+ve	0	0	0	0
Erected Fur	N	5	5	5	5
0 Not present	N+ve	5	5	5	5
1 Present	N+ve	0	0	0	0
Pupil Response	N	5	5	5	5
0 Normal constriction	N+ve	5	5	5	5
1 Partial/no constriction	N+ve	0	0	0	0
2 Pre-existing constriction	N+ve	0	0	0	0
Salivation	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Slight	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 8

22-Feb-2023 12:02:50

Summary of Neurobehavioral Evaluation: Autonomic

(b) (4)

Day: 86 Relative to Start Date (Pre)

Sex: Female		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
2 Severe	N+ve	0	0	0	0
Defecation	N	5	5	5	5
-1 Absent	N+ve	4	5	4	5
0 Normal	N+ve	1	0	1	0
1 Abnormal	N+ve	0	0	0	0
Palpebral Closure/Ptosis (HC)	N	5	5	5	5
0 Eyelids wide open	N+ve	5	5	5	5
1 Eyelids droop halfway	N+ve	0	0	0	0
2 Eyelids completely shut	N+ve	0	0	0	0
Palpebral Closure/Ptosis (OF)	N	5	5	5	5
0 Eyelids wide open	N+ve	5	5	5	5
1 Eyelids droop halfway	N+ve	0	0	0	0
2 Eyelids completely shut	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 9

22-Feb-2023 12:03:21

Summary of Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Day: 85 Relative to Start Date (Pre)

Sex: Male		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Gait/Mobility	N	5	5	5	5
0 Normal	N+ve	5	5	5	5
1 Slightly impaired	N+ve	0	0	0	0
2 Moderately impaired	N+ve	0	0	0	0
3 Severely impaired	N+ve	0	0	0	0
Forelimb Grip Strength Mean [G]	Mean	1053.73	1351.20	988.87	1070.20
	SD	326.63	217.18	315.66	265.04
	N	5	5	5	5
	%Diff	-	28.23	-6.16	1.56
Hindlimb Grip Strength Mean [G]	Mean	490.60	535.47	458.87	364.53
	SD	108.40	113.17	64.71	101.50
	N	5	5	5	5
	%Diff	-	9.15	-6.47	-25.70
Air Righting Reflex	N	5	5	5	5

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 9

22-Feb-2023 12:03:21

Summary of Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Day: 85 Relative to Start Date (Pre)

Sex: Male		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
0 Normal	N+ve	5	4	5	5
1 Abnormal	N+ve	0	1	0	0
2 Severely impaired	N+ve	0	0	0	0
Tremor (Home Cage)	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Slight	N+ve	0	0	0	0
2 Moderate	N+ve	0	0	0	0
3 Severe	N+ve	0	0	0	0
Tremor (Open Field)	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Slight	N+ve	0	0	0	0
2 Moderate	N+ve	0	0	0	0
3 Severe	N+ve	0	0	0	0
Body Tone	N	5	5	5	5

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 9

22-Feb-2023 12:03:21

Summary of Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Day: 85 Relative to Start Date (Pre)

Sex: Male		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
-1 Decreased	N+ve	0	0	0	0
0 Normal	N+ve	5	5	5	5
1 Increased	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 9

22-Feb-2023 12:03:21

Summary of Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Day: 86 Relative to Start Date (Pre)

Sex: Female		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Gait/Mobility	N	5	5	5	5
0 Normal	N+ve	5	5	5	5
1 Slightly impaired	N+ve	0	0	0	0
2 Moderately impaired	N+ve	0	0	0	0
3 Severely impaired	N+ve	0	0	0	0
Forelimb Grip Strength Mean [G]	Mean	827.40	926.27	977.40	887.67
	SD	519.86	380.75	289.49	291.37
	N	5	5	5	5
	%Diff	-	11.95	18.13	7.28
Hindlimb Grip Strength Mean [G]	Mean	493.33	516.00	437.73	443.73
	SD	65.45	74.35	74.63	83.56
	N	5	5	5	5
	%Diff	-	4.59	-11.27	-10.05
Air Righting Reflex	N	5	5	5	5

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 9

22-Feb-2023 12:03:21

Summary of Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Day: 86 Relative to Start Date (Pre)

Sex: Female		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
0 Normal	N+ve	5	5	5	5
1 Abnormal	N+ve	0	0	0	0
2 Severely impaired	N+ve	0	0	0	0
Tremor (Home Cage)	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Slight	N+ve	0	0	0	0
2 Moderate	N+ve	0	0	0	0
3 Severe	N+ve	0	0	0	0
Tremor (Open Field)	N	5	5	5	5
0 None	N+ve	5	5	5	5
1 Slight	N+ve	0	0	0	0
2 Moderate	N+ve	0	0	0	0
3 Severe	N+ve	0	0	0	0
Body Tone	N	5	5	5	5

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 9

22-Feb-2023 12:03:21

Summary of Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Day: 86 Relative to Start Date (Pre)

Sex: Female		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
-1 Decreased	N+ve	0	0	0	0
0 Normal	N+ve	5	5	5	5
1 Increased	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 10

22-Feb-2023 12:03:04

Summary of Neurobehavioral Evaluation: Sensorimotor

(b) (4)

Day: 85 Relative to Start Date (Pre)

Sex: Male		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Touch Resp/Tactile Reflex	N	5	5	5	5
-1 No reaction	N+ve	0	0	0	0
0 Normal reaction	N+ve	5	5	5	5
1 Exaggerated reaction	N+ve	0	0	0	0
Tail Pinch Response	N	5	5	5	5
-1 No reaction	N+ve	0	0	0	0
0 Normal Reaction	N+ve	5	5	5	5
1 Exaggerated reaction	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 10

22-Feb-2023 12:03:04

Summary of Neurobehavioral Evaluation: Sensorimotor

(b) (4)

Day: 86 Relative to Start Date (Pre)

Sex: Female		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Touch Resp/Tactile Reflex	N	5	5	5	5
-1 No reaction	N+ve	0	0	0	0
0 Normal reaction	N+ve	5	5	5	5
1 Exaggerated reaction	N+ve	0	0	0	0
Tail Pinch Response	N	5	5	5	5
-1 No reaction	N+ve	0	0	1	1
0 Normal Reaction	N+ve	5	5	4	4
1 Exaggerated reaction	N+ve	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 11

22-Feb-2023 12:03:09

Summary of Neurobehavioral Evaluation: Physiological

(b) (4)

Day: 85 Relative to Start Date (Pre)

Sex: Male		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Respiration	N	5	5	5	5
-1 Slowed	N+ve	0	0	0	0
0 Normal	N+ve	5	5	5	5
1 Rapid	N+ve	0	0	0	0
2 Abnormal	N+ve	0	0	0	0
Body Temperature (oC) [G]	Mean	36.54	36.46	35.84	36.32
	SD	0.98	0.81	0.61	0.31
	N	5	5	5	5
	%Diff	-	-0.22	-1.92	-0.60

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 11

22-Feb-2023 12:03:09

Summary of Neurobehavioral Evaluation: Physiological

(b) (4)

Day: 86 Relative to Start Date (Pre)

Sex: Female		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Respiration	N	5	5	5	5
-1 Slowed	N+ve	0	0	0	0
0 Normal	N+ve	5	5	5	5
1 Rapid	N+ve	0	0	0	0
2 Abnormal	N+ve	0	0	0	0
Body Temperature (oC) [G]	Mean	37.32	36.78	37.38	37.36
	SD	0.85	0.89	0.72	0.83
	N	5	5	5	5
	%Diff	-	-1.45	0.16	0.11

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 12

(b) (4)

Motor Activity - Fine Movements (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13

Males

Group 1, 0 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	583	493	-16%	282	-48%	130	-76%	321	-42%	364	-38%	2173
SD	171	178	13	51	21	94	18	162	31	212	30	516
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 2, 500 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	972*	557	-42%	250	-75%	175	-82%	320	-67%	209	-74%	2482
SD	317	235	17	265	22	106	10	243	24	159	28	837
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 3, 1000 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	691	482	-30%	355	-49%	352**	-48% *	328	-52%	326	-53%	2534
SD	97	143	20	158	23	43	12	200	30	170	20	570
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 4, 2000 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	1033*	510	-47%	533	-47%	484**	-51%	550	-44%	552	-44%	3661**
SD	236	64	20	194	18	181	21	313	34	224	26	477
N	5	5	5	5	5	5	5	5	5	5	5	5

*: $p \leq 0.05$; **: $p \leq 0.01$

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 12

(b) (4)

Motor Activity - Fine Movements (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13

Females

Group 1, 0 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	750	499	-30%	583	-22%	165	-80%	74	-86%	286	-61%	2356
SD	221	164	23	187	12	163	15	106	23	258	38	720
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 2, 500 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	659	399	-34%	249	-61%	194	-76%	234	-55%	151	-75%	1886
SD	217	80	25	136	22	194	22	182	40	156	30	316
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 3, 1000 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	624	486	-22%	364	-43%	108	-82%	89	-85%	128	-78%	1799
SD	65	86	14	322	47	110	19	42	8	131	25	367
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 4, 2000 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	621	450	-29%	516	-16%	269	-60%	303	-48%	267	-61%	2427
SD	154	219	33	259	39	251	28	214	40	190	22	763
N	5	5	5	5	5	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 12

(b) (4)

Motor Activity - Ambulation (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13

Males

Group 1, 0 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	108	75	-39%	27	-56%	10	-88%	42	-5%	58	-56%	320
SD	100	80	16	13	32	19	15	25	112	65	25	270
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 2, 500 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	250	103	-60%	48	-82%	30	-90%	43	-82%	38	-82%	512
SD	95	55	12	55	18	30	9	40	22	41	23	220
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 3, 1000 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	159	64	-58%	61	-60%	87**	-41% **	76	-46%	74	-55%	521
SD	50	41	25	34	27	25	21	51	35	41	17	160
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 4, 2000 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	230	70	-62%	97	-54%	65*	-64%	78	-61%	67	-68%	607
SD	88	58	40	52	23	47	29	43	27	31	15	173
N	5	5	5	5	5	5	5	5	5	5	5	5

*: $p \leq 0.05$; **: $p \leq 0.01$

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 12

(b) (4)

Motor Activity - Ambulation (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13

Females

Group 1, 0 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	231	130	-23%	122	-35%	3	-99%	12	-86%	59	-76%	556
SD	120	40	57	57	46	1	1	26	31	67	22	193
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 2, 500 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	200	107	-39%	35	-85%	50	-80%	53	-62%	32	-83%	476
SD	73	42	36	43	16	57	21	49	41	41	24	130
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 3, 1000 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	191	96	-49%	71	-62%	9	-93%	7	-97%	14	-90%	388
SD	43	17	5	57	27	17	14	12	6	19	15	83
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 4, 2000 mg/kg/day

	Interval										Total
	1	2		3		4		5		6	
Mean	147	129	-10%	134	1%	87	-40%	92	-33%	65	-61%	655
SD	56	85	80	103	69	60	42	100	69	61	34	208
N	5	5	5	5	5	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Male		Reporting Hematology						
		WBC (10^9/L) [G]	NEUT (%) [G]	LYMPH (%) [G]	MONO (%) [G]	EOS (%) [G]	BASO (%) [G]	LUC (%) [G1]
0	Mean	5.610	44.28	51.14	2.63	1.54	0.15	0.27
mg/kg	SD	1.340	8.80	8.63	0.59	0.59	0.07	0.14
/day	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
500	Mean	5.144	41.80	52.78	2.94	1.96	0.14	0.38
mg/kg	SD	1.277	8.10	8.04	0.73	0.75	0.07	0.30
/day	N	10	10	10	10	10	10	10
Group 2	tCtrl	0.92	0.94	1.03	1.12	1.27	0.93	1.41
1000	Mean	4.212	39.99	55.35	2.56	1.75	0.21	0.19
mg/kg	SD	1.747	8.46	7.88	0.85	0.73	0.19	0.09
/day	N	10	10	10	10	10	10	10
Group 3	tCtrl	0.75	0.90	1.08	0.97	1.14	1.40	0.70
2000	Mean	4.424	37.89	56.39	3.37	1.74	0.18	0.45
mg/kg	SD	1.226	8.66	7.71	0.96	0.86	0.10	0.30
/day	N	10	10	10	10	10	10	10
Group 4	tCtrl	0.79	0.86	1.10	1.28	1.13	1.20	1.67

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Male		Reporting Hematology						
		NEUT (10^9/L) [G]	LYMPH (10^9/L) [G]	MONO (10^9/L) [G]	EOS (10^9/L) [G]	BASO (10^9/L) [G]	LUC (10^9/L) [G1]	RBC (10^12/L) [G]
0	Mean	2.541	2.811	0.148	0.087	0.009	0.015	7.481
mg/kg	SD	0.957	0.596	0.053	0.040	0.006	0.007	0.545
/day	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
500	Mean	2.115	2.749	0.154	0.097	0.007	0.021	7.697
mg/kg	SD	0.518	0.982	0.054	0.030	0.005	0.023	0.267
/day	N	10	10	10	10	10	10	10
Group 2	tCtrl	0.83	0.98	1.04	1.11	0.78	1.40	1.03
1000	Mean	1.759	2.276	0.100	0.065	0.006	0.009	7.595
mg/kg	SD	0.999	0.828	0.043	0.031	0.005	0.003	0.452
/day	N	10	10	10	10	10	10	10
Group 3	tCtrl	0.69	0.81	0.68	0.75	0.67	0.60	1.02
2000	Mean	1.677	2.492	0.150	0.080	0.007	0.022	7.823
mg/kg	SD	0.590	0.771	0.060	0.049	0.005	0.019	0.351
/day	N	10	10	10	10	10	10	10
Group 4	tCtrl	0.66	0.89	1.01	0.92	0.78	1.47	1.05

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Male		Reporting Hematology						
		HGB (g/L) [G]	HCT (L/L) [G]	MCV (fL) [G1]	MCH (pg) [G]	MCHC (g/L) [G]	RDWG (%) [G]	PLT (10^9/L) [G]
0 mg/kg /day Group 1	Mean	132.3	0.4010	53.65	17.73	330.6	12.98	683.2
	SD	6.4	0.0259	1.75	0.77	9.6	0.75	78.8
	N	10	10	10	10	10	10	10
		.	-	-	-	-	-	-
500 mg/kg /day Group 2	Mean	134.5	0.4086	53.10	17.49	329.4	12.47	714.8
	SD	3.4	0.0144	0.88	0.38	5.3	0.39	78.1
	N	10	10	10	10	10	10	10
	tCtrl	1.02	1.02	0.99	0.99	1.00	0.96	1.05
1000 mg/kg /day Group 3	Mean	136.9	0.4134	54.53	18.05	331.3	12.19 **	671.2
	SD	7.3	0.0219	2.90	0.80	8.4	0.49	85.5
	N	10	10	10	10	10	10	10
	tCtrl	1.03	1.03	1.02	1.02	1.00	0.94	0.98
2000 mg/kg /day Group 4	Mean	136.0	0.4126	52.70	17.35	329.6	12.32 *	645.2
	SD	7.6	0.0244	1.64	0.57	6.7	0.46	80.7
	N	10	10	10	10	10	10	10
	tCtrl	1.03	1.03	0.98	0.98	1.00	0.95	0.94

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Male		Reporting Hematology		
		MPV (fL) [G]	RETIC (10^9/L) [G]	RETIC (%) [G]
0	Mean	8.32	183.85	2.45
mg/kg	SD	0.47	29.13	0.34
/day	N	10	10	10
Group 1		-	-	-
500	Mean	8.09	186.42	2.42
mg/kg	SD	0.50	29.29	0.35
/day	N	10	10	10
Group 2	tCtrl	0.97	1.01	0.99
1000	Mean	7.98	179.39	2.39
mg/kg	SD	0.30	22.47	0.37
/day	N	10	10	10
Group 3	tCtrl	0.96	0.98	0.98
2000	Mean	8.22	187.37	2.40
mg/kg	SD	0.54	19.08	0.22
/day	N	10	10	10
Group 4	tCtrl	0.99	1.02	0.98

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Female		Reporting Hematology						
		WBC (10^9/L) [G]	NEUT (%) [G]	LYMPH (%) [G]	MONO (%) [G]	EOS (%) [G]	BASO (%) [G]	LUC (%) [G]
0	Mean	3.600	33.19	62.40	2.64	1.34	0.09	0.36
mg/kg	SD	1.143	7.23	7.66	0.76	0.38	0.08	0.27
/day	N	9	9	9	9	9	9	9
Group 1		-	-	-	-	-	-	-
500	Mean	3.351	36.83	58.66	2.73	1.31	0.11	0.32
mg/kg	SD	0.998	8.73	8.78	0.73	0.41	0.11	0.14
/day	N	9	9	9	9	9	9	9
Group 2	tCtrl	0.93	1.11	0.94	1.03	0.98	1.25	0.91
1000	Mean	3.588	35.61	59.71	2.94	1.29	0.11	0.29
mg/kg	SD	1.263	8.44	8.62	0.71	0.40	0.06	0.13
/day	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.00	1.07	0.96	1.11	0.96	1.24	0.82
2000	Mean	4.290	25.32	70.24	2.85	0.97	0.13	0.46
mg/kg	SD	0.684	5.54	6.00	0.89	0.24	0.08	0.23
/day	N	10	10	10	10	10	10	10
Group 4	tCtrl	1.19	0.76	1.13	1.08	0.72	1.46	1.29

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Female		Reporting Hematology						
		NEUT (10^9/L) [G]	LYMPH (10^9/L) [G]	MONO (10^9/L) [G]	EOS (10^9/L) [G]	BASO (10^9/L) [G1]	LUC (10^9/L) [G]	RBC (10^12/L) [G]
0	Mean	1.167	2.272	0.094	0.049	0.001	0.016	6.587
mg/kg	SD	0.363	0.900	0.032	0.021	0.003	0.014	0.442
/day	N	9	9	9	9	9	9	9
Group 1		-	-	-	-	-	-	-
500	Mean	1.230	1.976	0.090	0.042	0.002	0.010	6.644
mg/kg	SD	0.425	0.692	0.028	0.016	0.004	0.005	0.326
/day	N	9	9	9	9	9	9	9
Group 2	tCtrl	1.05	0.87	0.95	0.86	2.00	0.64	1.01
1000	Mean	1.276	2.146	0.104	0.045	0.001	0.010	6.771
mg/kg	SD	0.534	0.868	0.042	0.016	0.003	0.008	0.626
/day	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.09	0.94	1.10	0.92	0.90	0.64	1.03
2000	Mean	1.089	3.018	0.120	0.040	0.004	0.018	6.908
mg/kg	SD	0.327	0.553	0.029	0.012	0.005	0.008	0.382
/day	N	10	10	10	10	10	10	10
Group 4	tCtrl	0.93	1.33	1.27	0.82	3.60	1.16	1.05

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Female		Reporting Hematology						
		HGB (g/L) [G]	HCT (L/L) [G]	MCV (fL) [G1]	MCH (pg) [G]	MCHC (g/L) [G1]	RDWG (%) [G]	PLT (10^9/L) [G]
0 mg/kg /day Group 1	Mean	123.1	0.3688	56.02	18.67	333.4	11.56	761.8
	SD	8.1	0.0238	0.78	0.59	6.9	0.45	33.8
	N	9	9	9	9	9	9	9
		.	-	-	-	-	-	-
500 mg/kg /day Group 2	Mean	119.1	0.3600	54.18	17.97	331.3	11.41	691.0
	SD	6.6	0.0220	2.07	0.71	3.8	0.43	122.1
	N	9	9	9	9	9	9	9
	tCtrl	0.97	0.98	0.97	0.96	0.99	0.99	0.91
1000 mg/kg /day Group 3	Mean	124.9	0.3770	55.79	18.51	331.8	11.29	668.8
	SD	8.7	0.0280	2.02	0.98	9.2	0.44	102.0
	N	10	10	10	10	10	10	10
	tCtrl	1.01	1.02	1.00	0.99	1.00	0.98	0.88
2000 mg/kg /day Group 4	Mean	124.9	0.3750	54.33	18.08	332.7	11.22	721.2
	SD	5.4	0.0189	1.77	0.58	3.3	0.48	94.0
	N	10	10	10	10	10	10	10
	tCtrl	1.01	1.02	0.97	0.97	1.00	0.97	0.95

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Female		Reporting Hematology		
		MPV (fL) [G]	RETIC (10^9/L) [G]	RETIC (%) [G]
0	Mean	8.16	181.94	2.76
mg/kg	SD	0.51	30.62	0.45
/day	N	9	9	9
Group 1		-	-	-
500	Mean	8.27	186.80	2.80
mg/kg	SD	0.54	17.35	0.27
/day	N	9	9	9
Group 2	tCtrl	1.01	1.03	1.02
1000	Mean	8.23	184.48	2.72
mg/kg	SD	0.76	26.34	0.27
/day	N	10	10	10
Group 3	tCtrl	1.01	1.01	0.99
2000	Mean	7.94	189.97	2.77
mg/kg	SD	0.40	30.07	0.45
/day	N	10	10	10
Group 4	tCtrl	0.97	1.04	1.01

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Male		Reporting Hematology						
		WBC (10^9/L) [G]	NEUT (%) [G]	LYMPH (%) [G1]	MONO (%) [G]	EOS (%) [G]	BASO (%) [G]	LUC (%) [G]
0	Mean	4.850	39.12	57.12	2.30	1.08	0.08	0.32
mg/kg	SD	1.401	4.73	4.70	0.87	0.40	0.04	0.16
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
2000	Mean	3.858	44.90	51.08	2.28	1.38	0.14	0.22
mg/kg	SD	0.965	10.94	10.41	0.59	0.53	0.15	0.04
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	0.80	1.15	0.89	0.99	1.28	1.75	0.69

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Male		Reporting Hematology						
		NEUT (10^9/L) [G]	LYMPH (10^9/L) [G]	MONO (10^9/L) [G]	EOS (10^9/L) [G1]	BASO (10^9/L) [G]	LUC (10^9/L) [G1]	RBC (10^12/L) [G]
0	Mean	1.864	2.808	0.110	0.046	0.004	0.016	7.418
mg/kg	SD	0.437	0.988	0.044	0.015	0.005	0.005	0.331
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
2000	Mean	1.796	1.912	0.090	0.050	0.002	0.010	7.552
mg/kg	SD	0.725	0.357	0.035	0.007	0.004	0.000	0.216
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	0.96	0.68	0.82	1.09	0.50	0.63	1.02

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Male		Reporting Hematology						
		HGB (g/L) [G]	HCT (L/L) [G]	MCV (fL) [G]	MCH (pg) [G]	MCHC (g/L) [G]	RDWG (%) [G]	PLT (10^9/L) [G]
0	Mean	131.8	0.3960	53.40	17.76	333.0	12.52	609.0
mg/kg	SD	7.9	0.0235	3.05	1.14	6.1	0.54	43.5
/day	N	5	5	5	5	5	5	5
Group 1		.	-	-	-	-	-	-
2000	Mean	133.0	0.4010	53.08	17.64	332.6	12.50	688.0
mg/kg	SD	3.9	0.0200	1.36	0.26	8.3	0.37	121.4
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.01	1.01	0.99	0.99	1.00	1.00	1.13

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Male		Reporting Hematology		
		MPV (fL) [G]	RETIC (10^9/L) [G]	RETIC (%) [G]
0	Mean	9.46	176.50	2.36
mg/kg	SD	0.19	23.96	0.30
/day	N	5	5	5
Group 1		-	-	-
2000	Mean	9.14	184.84	2.46
mg/kg	SD	0.27	13.46	0.21
/day	N	5	5	5
Group 4	tCtrl	0.97	1.05	1.04

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Female		Reporting Hematology						
		WBC (10^9/L) [G]	NEUT (%) [G]	LYMPH (%) [G]	MONO (%) [G]	EOS (%) [G]	BASO (%) [G]	LUC (%) [G]
0	Mean	3.840	34.90	60.06	3.12	1.34	0.18	0.40
mg/kg	SD	1.271	4.40	3.88	1.00	0.43	0.08	0.41
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
2000	Mean	3.842	40.30	55.48	2.80	0.88	0.10	0.48
mg/kg	SD	1.379	17.66	16.99	0.55	0.26	0.07	0.50
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.00	1.15	0.92	0.90	0.66	0.56	1.20

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Female		Reporting Hematology						
		NEUT (10^9/L) [G]	LYMPH (10^9/L) [G]	MONO (10^9/L) [G]	EOS (10^9/L) [G]	BASO (10^9/L) [G]	LUC (10^9/L) [G]	RBC (10^12/L) [G]
0	Mean	1.350	2.296	0.120	0.052	0.004	0.014	6.802
mg/kg	SD	0.516	0.714	0.054	0.026	0.005	0.011	0.234
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
2000	Mean	1.564	2.114	0.106	0.032	0.002	0.018	6.554
mg/kg	SD	0.844	1.060	0.042	0.013	0.004	0.022	0.352
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.16	0.92	0.88	0.62	0.50	1.29	0.96

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Female		Reporting Hematology						
		HGB (g/L) [G]	HCT (L/L) [G]	MCV (fL) [G]	MCH (pg) [G]	MCHC (g/L) [G]	RDWG (%) [G]	PLT (10^9/L) [G]
0	Mean	123.6	0.3686	54.20	18.18	335.4	11.00	749.0
mg/kg	SD	4.5	0.0153	1.86	0.62	5.1	0.38	35.2
/day	N	5	5	5	5	5	5	4
Group 1		.	-	-	-	-	-	-
2000	Mean	121.2	0.3600	55.02	18.52	337.2	11.26	666.4
mg/kg	SD	3.4	0.0120	2.26	0.67	5.1	0.23	71.7
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	0.98	0.98	1.02	1.02	1.01	1.02	0.89

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 13

24-Feb-2023 08:49:16

Summary of Hematology Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Female		Reporting Hematology		
		MPV (fL) [G]	RETIC (10^9/L) [G]	RETIC (%) [G]
0 mg/kg /day Group 1	Mean	8.86	159.74	2.36
	SD	0.36	13.67	0.18
	N	5	5	5
		-	-	-
2000 mg/kg /day Group 4	Mean	8.70	172.84	2.66
	SD	0.21	35.72	0.62
	N	5	5	5
	tCtrl	0.98	1.08	1.13

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 14

24-Feb-2023 08:44:34

Summary of Coagulation Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Male		Reporting Coagulation		
		PT (sec) [G]	APTT (sec) [G]	FIB (g/L) [G]
0	Mean	19.72	14.84	2.579
mg/kg	SD	1.41	1.73	0.189
/day	N	9	9	9
Group 1		-	-	.
500	Mean	20.78	14.85	2.764
mg/kg	SD	1.44	1.36	0.712
/day	N	10	10	10
Group 2	tCtrl	1.05	1.00	1.07
1000	Mean	20.48	14.68	2.620
mg/kg	SD	0.97	1.71	0.176
/day	N	8	8	8
Group 3	tCtrl	1.04	0.99	1.02
2000	Mean	21.58 **	15.16	2.608
mg/kg	SD	0.93	2.56	0.151
/day	N	9	9	9
Group 4	tCtrl	1.09	1.02	1.01

[G] - Anova & Dunnett: ** = $p \leq 0.01$

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 14

24-Feb-2023 08:44:34

Summary of Coagulation Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Female		Reporting Coagulation		
		PT (sec) [G]	APTT (sec) [G1]	FIB (g/L) [G]
0	Mean	20.52	16.45	1.861
mg/kg	SD	0.90	0.87	0.265
/day	N	10	10	10
Group 1		-	-	.
500	Mean	20.22	15.48	1.924
mg/kg	SD	0.81	1.46	0.171
/day	N	10	10	10
Group 2	tCtrl	0.99	0.94	1.03
1000	Mean	19.70	14.31 *	1.888
mg/kg	SD	1.75	1.92	0.248
/day	N	9	9	9
Group 3	tCtrl	0.96	0.87	1.01
2000	Mean	20.49	14.41 *	1.959
mg/kg	SD	1.37	2.11	0.411
/day	N	9	9	9
Group 4	tCtrl	1.00	0.88	1.05

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn: * = $p \leq 0.05$

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 14

24-Feb-2023 08:44:34

Summary of Coagulation Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Male		Reporting Coagulation		
		PT (sec) [G]	APTT (sec) [G]	FIB (g/L) [G]
0	Mean	18.78	17.20	2.574
mg/kg	SD	1.71	0.35	0.201
/day	N	5	5	5
Group 1		-	-	.
2000	Mean	18.98	16.80	2.352
mg/kg	SD	0.63	0.77	0.227
/day	N	5	5	5
Group 4	tCtrl	1.01	0.98	0.91

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 14

24-Feb-2023 08:44:34

Summary of Coagulation Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Female		Reporting Coagulation		
		PT (sec) [G]	APTT (sec) [G]	FIB (g/L) [G]
0	Mean	20.28	17.16	1.738
mg/kg	SD	0.43	0.60	0.104
/day	N	5	5	5
Group 1		-	-	.
2000	Mean	20.14	16.88	1.850
mg/kg	SD	0.82	0.54	0.182
/day	N	5	5	5
Group 4	tCtrl	0.99	0.98	1.06

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Male		Reporting Biochemistry						
		AST (U/L) [G]	ALT (U/L) [G]	ALP (U/L) [G]	GGT (U/L) [G1]	TBIL (umol/L) [G]	BILEAC (umol/L) [G]	UREA (mmol/L) [G]
0	Mean	86.1	27.8	58.8	2.0	2.88	15.96	7.54
mg/kg	SD	10.8	6.1	11.2	0.0	0.34	9.23	0.74
/day	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
500	Mean	94.3	33.8	62.6	2.0	2.71	18.08	6.88
mg/kg	SD	23.0	24.9	13.7	0.0	0.33	10.64	1.11
/day	N	10	10	10	10	10	10	10
Group 2	tCtrl	1.10	1.22	1.06	1.00	0.94	1.13	0.91
1000	Mean	91.2	31.7	58.6	2.0	2.63	16.10	6.64
mg/kg	SD	17.6	9.5	10.6	0.0	0.31	14.51	0.68
/day	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.06	1.14	1.00	1.00	0.91	1.01	0.88
2000	Mean	96.8	31.2	59.8	2.0	2.61	12.88	6.77
mg/kg	SD	14.5	7.8	8.8	0.0	0.38	12.85	1.05
/day	N	10	10	10	10	10	10	10
Group 4	tCtrl	1.12	1.12	1.02	1.00	0.91	0.81	0.90

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Male		Reporting Biochemistry						
		CREAT (umol/L) [G]	GLUC (mmol/L) [G1]	CHOL (mmol/L) [G1]	HDL (mmol/L) [G1]	LDL (mmol/L) [G1]	TRIG (mmol/L) [G]	TPROT (g/L) [G]
0	Mean	45.1	8.870	1.753	0.457	0.360	1.149	58.21
mg/kg	SD	3.8	1.181	0.457	0.111	0.000	0.785	2.44
/day	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
500	Mean	43.4	8.606	1.709	0.491	0.360	1.001	57.29
mg/kg	SD	3.1	1.145	0.410	0.124	0.000	0.308	3.08
/day	N	10	10	10	10	10	10	10
Group 2	tCtrl	0.96	0.97	0.97	1.07	1.00	0.87	0.98
1000	Mean	41.7	9.400	1.757	0.488	0.360	1.055	57.40
mg/kg	SD	3.3	2.288	0.209	0.058	0.000	0.213	2.96
/day	N	10	10	10	10	10	10	10
Group 3	tCtrl	0.92	1.06	1.00	1.07	1.00	0.92	0.99
2000	Mean	40.8 *	9.655	1.534	0.457	0.360	0.963	57.92
mg/kg	SD	2.7	1.561	0.158	0.043	0.000	0.192	3.24
/day	N	10	10	10	10	10	10	10
Group 4	tCtrl	0.90	1.09	0.88	1.00	1.00	0.84	1.00

[G] - Anova & Dunnett: * = $p \leq 0.05$
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Male		Reporting Biochemistry						
		ALB (g/L) [G]	GLOB (g/L) [G]	A/G (ratio) [G1]	CA (mmol/L) [G]	NA (mmol/L) [G]	K (mmol/L) [G]	CL (mmol/L) [G1]
0	Mean	32.20	26.01	1.24	2.548	141.2	4.10	103.1
mg/kg	SD	1.12	1.58	0.07	0.065	1.0	0.21	1.2
/day	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
500	Mean	31.72	25.57	1.25	2.567	141.1	4.35 *	102.7
mg/kg	SD	1.58	1.74	0.07	0.070	1.5	0.16	1.6
/day	N	10	10	10	10	10	10	10
Group 2	tCtrl	0.99	0.98	1.01	1.01	1.00	1.06	1.00
1000	Mean	32.15	25.25	1.28	2.558	141.2	4.31	103.2
mg/kg	SD	1.47	1.57	0.04	0.042	1.8	0.30	1.4
/day	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.00	0.97	1.03	1.00	1.00	1.05	1.00
2000	Mean	32.12	25.80	1.25	2.530	140.8	4.39 *	102.5
mg/kg	SD	1.27	2.41	0.10	0.055	1.5	0.21	3.0
/day	N	10	10	10	10	10	10	10
Group 4	tCtrl	1.00	0.99	1.01	0.99	1.00	1.07	0.99

[G] - Anova & Dunnett: * = $p \leq 0.05$
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Male		Reporting Biochem
		PHOS (mmol/L) [G]
0 mg/kg /day Group 1	Mean	2.252
	SD	0.258
	N	10
		-
500 mg/kg /day Group 2	Mean	2.166
	SD	0.359
	N	10
	tCtrl	0.96
1000 mg/kg /day Group 3	Mean	2.124
	SD	0.451
	N	10
	tCtrl	0.94
2000 mg/kg /day Group 4	Mean	2.052
	SD	0.335
	N	10
	tCtrl	0.91

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Female		Reporting Biochemistry						
		AST (U/L) [G]	ALT (U/L) [G]	ALP (U/L) [G]	GGT (U/L) [G1]	TBIL (umol/L) [G]	BILEAC (umol/L) [G]	UREA (mmol/L) [G]
0	Mean	103.9	24.5	37.7	2.0	3.41	26.05	7.42
mg/kg	SD	15.8	7.4	13.3	0.0	0.39	20.18	1.93
/day	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
500	Mean	98.4	20.5	37.9	2.0	3.01	23.85	6.93
mg/kg	SD	19.8	3.3	9.9	0.0	0.27	14.93	1.40
/day	N	10	10	10	10	10	10	10
Group 2	tCtrl	0.95	0.84	1.01	1.00	0.88	0.92	0.93
1000	Mean	105.5	24.8	37.5	2.0	3.47	22.22	6.62
mg/kg	SD	16.8	4.1	18.2	0.0	0.76	12.72	1.31
/day	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.02	1.01	0.99	1.00	1.02	0.85	0.89
2000	Mean	98.7	26.5	54.5	2.0	3.84	32.58	6.93
mg/kg	SD	26.9	6.0	21.5	0.0	0.57	21.07	1.23
/day	N	10	10	10	10	10	10	10
Group 4	tCtrl	0.95	1.08	1.45	1.00	1.13	1.25	0.93

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Female		Reporting Biochemistry						
		CREAT (umol/L) [G]	GLUC (mmol/L) [G]	CHOL (mmol/L) [G]	HDL (mmol/L) [G]	LDL (mmol/L) [G1]	TRIG (mmol/L) [G]	TPROT (g/L) [G1]
0	Mean	43.6	8.527	1.426	0.444	0.360	0.356	62.00
mg/kg	SD	4.5	1.909	0.325	0.113	0.000	0.089	2.39
/day	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
500	Mean	43.8	7.721	1.716	0.498	0.360	0.498	61.35
mg/kg	SD	3.2	1.163	0.457	0.118	0.000	0.137	1.57
/day	N	10	10	10	10	10	10	10
Group 2	tCtrl	1.00	0.91	1.20	1.12	1.00	1.40	0.99
1000	Mean	41.5	7.460	1.765	0.522	0.360	0.501	63.50
mg/kg	SD	3.3	2.156	0.322	0.106	0.000	0.169	5.05
/day	N	10	10	10	10	10	10	10
Group 3	tCtrl	0.95	0.87	1.24	1.18	1.00	1.41	1.02
2000	Mean	39.7 *	8.176	1.583	0.481	0.360	0.468	61.65
mg/kg	SD	2.3	2.179	0.380	0.118	0.000	0.130	1.90
/day	N	10	10	10	10	10	10	10
Group 4	tCtrl	0.91	0.96	1.11	1.08	1.00	1.31	0.99

[G] - Anova & Dunnett: * = $p \leq 0.05$
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Female		Reporting Biochemistry						
		ALB (g/L) [G]	GLOB (g/L) [G1]	A/G (ratio) [G1]	CA (mmol/L) [G1]	NA (mmol/L) [G1]	K (mmol/L) [G1]	CL (mmol/L) [G1]
0	Mean	35.90	26.10	1.37	2.600	139.2	4.10	103.0
mg/kg	SD	1.54	1.62	0.11	0.070	1.6	0.15	1.8
/day	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
500	Mean	35.05	26.30	1.34	2.575	140.1	3.94	102.8
mg/kg	SD	1.29	1.02	0.08	0.066	2.0	0.26	1.9
/day	N	10	10	10	10	10	10	10
Group 2	tCtrl	0.98	1.01	0.98	0.99	1.01	0.96	1.00
1000	Mean	36.32	27.18	1.33	2.626	140.9	4.19	104.4
mg/kg	SD	3.64	1.80	0.09	0.075	1.8	0.38	1.6
/day	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.01	1.04	0.97	1.01	1.01	1.02	1.01
2000	Mean	35.33	26.32	1.36	2.611	141.6 **	4.07	104.1
mg/kg	SD	1.61	1.32	0.11	0.053	1.3	0.23	1.0
/day	N	10	10	10	10	10	10	10
Group 4	tCtrl	0.98	1.01	0.99	1.00	1.02	0.99	1.01

[G] - Kruskal-Wallis & Dunn
[G1] - Anova & Dunnett: ** = $p \leq 0.01$

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Female		Reporting Biochem
		PHOS (mmol/L) [G]
0 mg/kg /day Group 1	Mean	1.972
	SD	0.219
	N	10
		-
500 mg/kg /day Group 2	Mean	1.848
	SD	0.188
	N	10
	tCtrl	0.94
1000 mg/kg /day Group 3	Mean	2.053
	SD	0.272
	N	10
	tCtrl	1.04
2000 mg/kg /day Group 4	Mean	2.267 *
	SD	0.192
	N	10
	tCtrl	1.15

[G] - Anova & Dunnett: * = $p \leq 0.05$

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Male		Reporting Biochemistry						
		AST (U/L) [G]	ALT (U/L) [G]	ALP (U/L) [G]	GGT (U/L) [G1]	TBIL (umol/L) [G]	BILEAC (umol/L) [G]	UREA (mmol/L) [G]
0	Mean	84.0	28.6	44.6	2.0	2.78	31.38	7.30
mg/kg	SD	11.3	8.2	6.8	0.0	0.28	11.75	0.80
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
2000	Mean	88.6	28.8	49.2	2.0	2.52	17.80	7.50
mg/kg	SD	13.9	12.9	9.6	0.0	0.22	10.35	0.94
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.05	1.01	1.10	1.00	0.91	0.57	1.03

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Male		Reporting Biochemistry						
		CREAT (umol/L) [G]	GLUC (mmol/L) [G]	CHOL (mmol/L) [G]	HDL (mmol/L) [G]	LDL (mmol/L) [G1]	TRIG (mmol/L) [G]	TPROT (g/L) [G]
0	Mean	45.4	8.648	1.700	0.464	0.360	0.584	56.44
mg/kg	SD	4.4	1.616	0.469	0.094	0.000	0.127	2.23
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
2000	Mean	42.6	8.596	1.620	0.442	0.360	0.640	54.84
mg/kg	SD	4.2	0.967	0.093	0.036	0.000	0.151	1.17
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	0.94	0.99	0.95	0.95	1.00	1.10	0.97

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Male		Reporting Biochemistry						
		ALB (g/L) [G]	GLOB (g/L) [G]	A/G (ratio) [G1]	CA (mmol/L) [G]	NA (mmol/L) [G]	K (mmol/L) [G]	CL (mmol/L) [G]
0	Mean	31.32	25.12	1.26	2.510	141.6	4.24	104.0
mg/kg	SD	0.66	1.75	0.09	0.089	1.3	0.36	1.6
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
2000	Mean	30.62	24.22	1.30	2.494	142.8	4.22	105.4
mg/kg	SD	0.53	0.66	0.00	0.059	1.1	0.23	0.5
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	0.98	0.96	1.03	0.99	1.01	1.00	1.01

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Male		Reporting Biochem
		PHOS (mmol/L) [G]
0 mg/kg /day Group 1	Mean	2.172
	SD	0.324
	N	5
		-
2000 mg/kg /day Group 4	Mean	2.134
	SD	0.330
	N	5
	tCtrl	0.98

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Female		Reporting Biochemistry						
		AST (U/L) [G]	ALT (U/L) [G1]	ALP (U/L) [G1]	GGT (U/L) [G]	TBIL (umol/L) [G1]	BILEAC (umol/L) [G1]	UREA (mmol/L) [G1]
0	Mean	72.0	17.8	31.2	2.0	3.30	46.26	7.10
mg/kg	SD	6.0	3.6	8.6	0.0	0.31	19.54	1.25
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
2000	Mean	113.8	26.6	35.0	2.0	3.36	84.00	8.26
mg/kg	SD	37.5	9.5	18.5	0.0	0.52	118.78	2.21
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.58	1.49	1.12	1.00	1.02	1.82	1.16

[G] - Kruskal-Wallis & Dunn
[G1] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Female		Reporting Biochemistry						
		CREAT (umol/L) [G]	GLUC (mmol/L) [G]	CHOL (mmol/L) [G1]	HDL (mmol/L) [G]	LDL (mmol/L) [G1]	TRIG (mmol/L) [G]	TPROT (g/L) [G]
0	Mean	43.8	8.416	1.278	0.432	0.360	0.384	62.06
mg/kg	SD	1.9	1.053	0.201	0.071	0.000	0.084	2.80
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
2000	Mean	44.6	8.484	1.554	0.492	0.360	0.354	59.06
mg/kg	SD	3.4	1.610	0.467	0.112	0.000	0.042	1.51
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.02	1.01	1.22	1.14	1.00	0.92	0.95

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Female		Reporting Biochemistry						
		ALB (g/L) [G]	GLOB (g/L) [G]	A/G (ratio) [G]	CA (mmol/L) [G]	NA (mmol/L) [G]	K (mmol/L) [G]	CL (mmol/L) [G]
0	Mean	36.56	25.50	1.42	2.562	140.8	3.98	103.2
mg/kg	SD	1.62	1.50	0.08	0.094	0.8	0.44	0.8
/day	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
2000	Mean	33.56 **	25.50	1.32 *	2.568	139.2 *	4.10	103.0
mg/kg	SD	1.09	1.00	0.04	0.029	0.8	0.24	0.7
/day	N	5	5	5	5	5	5	5
Group 4	tCtrl	0.92	1.00	0.93	1.00	0.99	1.03	1.00

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 15

16-Mar-2023 08:12:01

Summary of Clinical Chemistry Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Female		Reporting Biochem
		PHOS (mmol/L) [G]
0 mg/kg /day Group 1	Mean	1.818
	SD	0.143
	N	5
		-
2000 mg/kg /day Group 4	Mean	2.010
	SD	0.309
	N	5
	tCtrl	1.11

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 16

24-Feb-2023 08:45:05

Summary of Urinalysis Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Male		Reporting Urinalysis			
		VOLUME (mL) [G]	SPECIFIC GRAVITY [G]	OSMLTY (mOsm/kg) [G]	URINE pH [G]
0	Mean	17.91	1.0175	568.6	7.80
mg/kg	SD	7.66	0.0067	252.4	0.67
/day	N	10	10	10	10
Group 1		-	-	-	-
500	Mean	16.53	1.0199	627.4	7.40
mg/kg	SD	5.04	0.0078	249.7	0.70
/day	N	10	10	10	10
Group 2	tCtrl	0.92	1.00	1.10	0.95
1000	Mean	16.24	1.0201	591.2	6.70 **
mg/kg	SD	5.07	0.0053	184.5	0.54
/day	N	10	10	10	10
Group 3	tCtrl	0.91	1.00	1.04	0.86
2000	Mean	19.08	1.0251	694.8	5.45 **
mg/kg	SD	14.24	0.0081	265.4	0.50
/day	N	10	10	10	10
Group 4	tCtrl	1.07	1.01	1.22	0.70

[G] - Anova & Dunnett: ** = $p \leq 0.01$

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 16

24-Feb-2023 08:45:05

Summary of Urinalysis Values

(b) (4)

Day: 91 Relative to Start Date

Sex: Female		Reporting Urinalysis			
		VOLUME (mL) [G]	SPECIFIC GRAVITY [G]	OSMLTY (mOsm/kg) [G]	URINE pH [G]
0	Mean	14.32	1.0174	614.0	6.95
mg/kg	SD	7.84	0.0069	247.0	0.72
/day	N	10	10	10	10
Group 1		-	-	-	-
500	Mean	12.15	1.0227	780.4	6.65
mg/kg	SD	6.92	0.0101	379.7	0.63
/day	N	10	10	10	10
Group 2	tCtrl	0.85	1.01	1.27	0.96
1000	Mean	14.25	1.0217	698.2	6.40
mg/kg	SD	7.87	0.0092	340.7	0.61
/day	N	10	10	10	10
Group 3	tCtrl	1.00	1.00	1.14	0.92
2000	Mean	18.41	1.0256	601.0	5.75 **
mg/kg	SD	11.30	0.0158	329.2	0.35
/day	N	10	10	10	10
Group 4	tCtrl	1.29	1.01	0.98	0.83

[G] - Anova & Dunnett: ** = $p \leq 0.01$

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 16

24-Feb-2023 08:45:05

Summary of Urinalysis Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Male		Reporting Urinalysis			
		VOLUME (mL) [G]	SPECIFIC GRAVITY [G]	OSMLTY (mOsm/kg) [G]	URINE pH [G]
0	Mean	19.28	1.0162	513.2	7.10
mg/kg	SD	5.87	0.0075	260.4	0.42
/day	N	5	5	5	5
Group 1		-	-	-	-
2000	Mean	13.94	1.0228	713.2	6.90
mg/kg	SD	8.85	0.0135	501.8	0.74
/day	N	5	5	5	5
Group 4	tCtrl	0.72	1.01	1.39	0.97

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Table 16

24-Feb-2023 08:45:05

Summary of Urinalysis Values

(b) (4)

Day: 120 Relative to Start Date

Sex: Female		Reporting Urinalysis			
		VOLUME (mL) [G]	SPECIFIC GRAVITY [G]	OSMLTY (mOsm/kg) [G]	URINE pH [G]
0	Mean	10.58	1.0206	680.8	6.60
mg/kg	SD	3.93	0.0075	319.1	0.22
/day	N	5	5	5	5
Group 1		-	-	-	-
2000	Mean	12.64	1.0200	626.4	6.30
mg/kg	SD	6.47	0.0076	253.3	0.45
/day	N	5	5	5	5
Group 4	tCtrl	1.19	1.00	0.92	0.95

[G] - Anova & Dunnett

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 17

(b) (4)

Mean Sperm Motility Data - Main Males

(From the Epididymis)

Dose Level		Total Number of Sperm	Motile Sperm		Progressive Sperm	
			Count	(%)	Count	(%)
0 mg/kg/day	MEAN	1041	1019	97	750	72
	SD	276	283	2	200	4
	N	10	10	10	10	10
500 mg/kg/day	MEAN	976	953	97	701	73
	SD	417	416	2	286	4
	N	10	10	10	10	10
1000 mg/kg/day	MEAN	952	935	98	695	73
	SD	406	405	2	302	5
	N	10	10	10	10	10
2000 mg/kg/day	MEAN	1340	1321	99	938	71
	SD	373	369	1	248	6
	N	9	9	9	9	9

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 17

(b) (4)

Mean Sperm Counts - Main Males
(From the Testis)

Dose Level		Testis Weight (g)	Millions / Gram Testis
0 mg/kg/day	MEAN	1.869	102.7
	SD	0.149	32.4
	N	10	10
500 mg/kg/day	MEAN	1.812	114.5
	SD	0.179	37.8
	N	10	10
1000 mg/kg/day	MEAN	1.816	120.0
	SD	0.120	29.9
	N	10	10
2000 mg/kg/day	MEAN	1.697	129.1
	SD	0.103	33.1
	N	9	9

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 17

(b) (4)

Mean Sperm Counts - Main Males
(From the Cauda Epididymis)

Dose Level		Cauda Epididymis Weight (g)	Millions / Gram Cauda Epididymis
0 mg/kg/day	MEAN	0.273	436.0
	SD	0.016	124.3
	N	10	10
500 mg/kg/day	MEAN	0.275	375.9
	SD	0.022	125.9
	N	10	10
1000 mg/kg/day	MEAN	0.274	434.5
	SD	0.029	152.6
	N	10	10
2000 mg/kg/day	MEAN	0.264	421.6
	SD	0.017	80.3
	N	9	9

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 17

(b) (4)

Mean Sperm Motility Data - Recovery Males

(From the Epididymis)

Dose Level		Total Number of Sperm	Motile Sperm		Progressive Sperm	
			Count	(%)	Count	(%)
0 mg/kg/day	MEAN	1343	1282	95	911	69
	SD	425	407	1	248	5
	N	5	5	5	5	5
2000 mg/kg/day	MEAN	697*	663*	94	514*	74
	SD	414	407	4	289	4
	N	5	5	5	5	5

*: $p \leq 0.05$.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 17

(b) (4)

Mean Sperm Counts - Recovery Males

(From the Testis)

Dose Level		Testis Weight (g)	Millions / Gram Testis
0 mg/kg/day	MEAN	2.039	98.8
	SD	0.132	34.4
	N	5	5
2000 mg/kg/day	MEAN	1.825	117.7
	SD	0.181	84.4
	N	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 17

(b) (4)

Mean Sperm Counts - Recovery Males
(From the Cauda Epididymis)

Dose Level		Cauda Epididymis Weight (g)	Millions / Gram Cauda Epididymis
0 mg/kg/day	MEAN	0.351	391.1
	SD	0.033	96.8
	N	5	5
2000 mg/kg/day	MEAN	0.305*	501.1
	SD	0.023	132.3
	N	5	5

*: $p \leq 0.05$.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 18

24-Feb-2023 08:44:52

Summary of Sperm Morphology Evaluation: Main Males

(b) (4)

Sex: Male Day(s) Relative to Start Date			0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Normal Sperm	91 [k]	Mean	179.5	176.1
		SD	8.2	7.0
		N	10	9
		%Diff	-	-1.9
Abnormal Head(s)	91 [k]	Mean	0.4	0.7
		SD	0.5	1.0
		N	10	9
Detached Head	91 [k]	Mean	0.6	0.8
		SD	0.7	1.1
		N	10	9
Abnormal Midpiece	91 [k]	Mean	0.2	0.2
		SD	0.4	0.4
		N	10	9
Abnormal Tail(s)	91 [k]	Mean	1.5	1.2
		SD	2.4	1.0
		N	10	9
Coiled Tail	91 [k]	Mean	17.6	20.9
		SD	7.8	6.1
		N	10	9
Abnormal Sperm Combo	91 [k]	Mean	0.2	0.1
		SD	0.4	0.3
		N	10	9

[k] - Dunn

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Table 18

24-Feb-2023 08:44:52

Summary of Sperm Morphology Evaluation: Recovery Males

(b) (4)

Sex: Male Day(s) Relative to Start Date			0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Normal Sperm	120 [k]	Mean	170.8	171.0
		SD	5.0	5.0
		N	5	5
		%Diff	-	0.1
Abnormal Head(s)	120 [k]	Mean	0.0	0.6
		SD	0.0	0.5
		N	5	5
Detached Head	120 [k]	Mean	1.6	1.0
		SD	1.1	0.7
		N	5	5
Abnormal Midpiece	120 [k]	Mean	0.6	0.4
		SD	0.5	0.5
		N	5	5
Abnormal Tail(s)	120 [k]	Mean	0.8	1.4
		SD	1.3	0.9
		N	5	5
Coiled Tail	120 [k]	Mean	26.2	25.4
		SD	3.1	4.8
		N	5	5
Abnormal Sperm Combo	120 [k]	Mean	0.0	0.2
		SD	0.0	0.4
		N	5	5

[k] - Dunn

Appendix 1

DEVIATIONS

All deviations that occurred during the study have been authorized/acknowledged by the Study Director, assessed for impact, and documented in the study records. All Study Plan deviations and those SOP deviations that could have impacted the quality or integrity of the study are listed below. Minor SOP deviations that did not impact the quality or integrity of the study have been included at the discretion of the Study Director.

Terminal Procedures

- One eye from Female No. 4504 (2000 mg/kg/day) was inadvertently thrown away in a solvent tank at the time of the fixative change (from Davidson's fixative to 70% ethanol) and could potentially have been in contact with solvents other than Davidson or 70% ethanol for a few hours. The eye was placed in 70% ethanol after specific identification for differentiation from the other eye. There was no impact of this incident on the quality of the slide. The Pathologist has evaluated the sample and thus there was no impact on study conclusions.

Statistical Analysis

- Statistical analysis of hormones data was performed at the Test Facility instead of at the Test Site as indicated in the Study Plan. As the statistical analysis was still performed according to the Study Plan indications, this deviation had no impact on the study interpretation and conclusions.

Test Materials

- The designation of the test item report has been redefined at the request of the Sponsor for consistency in the EFSA application dossier. It replaces the initial test item name. The title of the study has been modified to reflect this change.
- Initial test item name: TRP Pro // New test item name: L-Tryptophan (TRP Pro)

  Nevertheless, there are multiple occasions during the study conduct when the test item designation as per Study Plan has been used in the study documentation, data, and phase reports. This deviation is considered to have no impact on the study data integrity and achievement of study objectives as the new designation was in the Study Plan as "alternate identification" of the test item. Therefore, it is acceptable to use either of the test item denominations as described in the Study Plan.

Regulatory Compliance

- Error in the Study Plan Section 16. Regulatory compliance: the date of 16 Oct 2007 is not accurate for the «Good Laboratory Practices in Article Annexe II de l'article D523-8 du code de l'environnement» and was therefore deleted from the GLP statement of the study report. This error had no impact on the study objectives and outcome as the study was conducted as appropriate and in compliance with the regulation.

None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

There were no deviations in the Phase Reports that were considered by the Study Director to have affected the outcome or the achievement of the study objectives.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 1

(b) (4)

STUDY PLAN AMENDMENT No. 04

Test Facility Study No. (b) (4)

Sponsor Reference No. (b) (4)

90-Day Repeated Dose Toxicity Study of TRP Pro by the Oral (gavage) Route in the Wistar Han IGS Rat With a 4-Week Recovery Period

(b) (4) Study

SPONSOR:
CJ CheilJedang Corporation
55-42 Beongil Gwanggyo-ro, Yeongtong-gu
Suwon-si
16495 Gyeonggi-do
Republic of Korea

TEST FACILITY:
(b) (4)

Appendix 1

SUMMARY OF CHANGES AND JUSTIFICATIONS

Note: when applicable, additions are indicated in **bold underlined** and deletions are indicated in ~~strikethrough~~ text in the concerned sections.

Item/Section(s)	Reason for amendment
Final Study Plan	**Date: 04 Oct 2022**
Amendment 1	**Date: 12 Oct 2022**
5.2. Test Material Identification	To add a second alternate identification.
9.1. Administration of the Test and Control Materials	To correct the title of the section.
11.1. Sample Collection	To correct typographical errors.
11.2. Hematology	
11.5. Urinalysis	
13.1. Histology	To precise that sperm analysis will be performed for all groups.
14.3. Inferential Statistical Methods	To add the (b) (4) Monitor to the list of inferential statistical methods.
Amendment 2	**Date: 10 Nov 2022**
5.2. Test Material Identification	To add precisions regarding the test item identification.
6.3. Sample Collection and Analysis	To correct the storage condition of the formulation sample at the Test Site.
10. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS	To add precision regarding the estrous cycles.
10.4. Estrous Cycles	
11.7.3. Acceptance criteria	To correct a typographical error.
16. REGULATORY COMPLIANCE	To correct the references used for regulatory compliance.

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Amendment 3	**Date: 08 Dec 2022**
6.1. Preparation of Formulations	To add precisions regarding the storage of the test item formulations. To update the stability data of the formulations according to the analytical validation study 21/300-316AN.
6.3. Sample Collection and Analysis	To add an additional sample for dose formulation analysis on Week 13.
ATTACHMENT B	To update the samples to be shipped for dose formulation analysis.
Amendment 4	**Current version**
14.5. Non-Parametric 14.6. For Data Generated Outside (b) (4)	To update the statistical methods for datasets intended to include only two groups.

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Appendix 1

1. OBJECTIVE(S)

The objective of this study is to determine the potential toxicity of TRP Pro when given by the oral (gavage) route for 90 days to the Wistar Han IGS rat and to evaluate the potential reversibility of any findings after a 4-week recovery period.

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual dates will be included in the Final Report.

Animal Arrival:	10 Oct 2022.
Experimental Starting Date:	10 Oct 2022.
Initiation of Dosing:	18 Oct 2022.
Completion of In-Life:	End of Dosing Period: 16 and 17 Jan 2023. End of Recovery Period: 14 Feb 2023.
Experimental Completion Date:	03 Oct 2023. (last date on which data are collected).
Data Review Meeting:	Week of 24 Apr 2023.
Draft Report:	09 May 2023.
Consolidated Sponsor Comments:	09 Jun 2023.
Unsigned Final Report:	03 Oct 2023. This date is dependent on the date of receipt of Sponsor comments and final contributing Phase Reports. Any delay may have repercussions on the issue date of the Final Draft Report.
Final Report:	24 Oct 2023 (expected date of Study Director signature of report).

The contributions from Principal Investigators to Study Director are proposed at the dates indicated below to allow inclusion in the Draft Study Report.

Dose Formulation Analysis Draft Report:	07 Apr 2023.
Dose Formulation Analysis Final Report:	01 Sep 2023.
Thyroid Hormone Analysis Draft Report:	07 Apr 2023.
Thyroid Hormone Analysis Final Report:	01 Sep 2023.

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3. SPONSOR

Role	Name	Contact Information
Sponsor Study Monitor/Representative Name	(b)(6)	Address as cited for Sponsor Tel: + (b)(6) E-mail: (b)(6)

4. RESPONSIBLE PERSONNEL

Role/Phase	Quality Assurance Unit	Name	Contact Information
Study Director			(b) (4), (b)(6)
Alternative Contact			
Test Facility Management			
Test Facility Lead QA			
Individual Scientist (IS)			
Ophthalmology			(b) (4), (b)(6)
Safety Pharmacologist			
Study Pathologist			

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Principal Investigators (PI)	
Formulation Analysis (Phase No. 21/300-420AN)[a]	(b) (4), (b)(6)
T3, T4, TSH hormone measurement (Phase No. 21/300-430AN)[a]	
Test Site QAU	

[a] Test Site selected by the Study Director in agreement with the Study Sponsor.

Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner for authorization/acknowledgement. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report.

The Phase Report will include the following:

- A statement of compliance.
- A QA statement.
- The archive site for all records, samples, specimens, and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report).
- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase.

5. TEST MATERIALS

5.1. Test Material Characterization

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity, composition, and stability for the test item(s) provided. A certificate of analysis or equivalent documentation will be provided for inclusion in the Final Report. The Sponsor will also provide information concerning the regulatory standard (GLP, GMP, or other) followed for these evaluations.

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The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the test item(s) provided, and this information is available to the appropriate regulatory agencies should it be requested.

5.2. Test Material Identification

Test Item Identification

	Test Item
Identification:	TRP Pro
Alternate identification	L-tryptophan (TRP Pro) / Tryptophan (TRP Pro)
Batch/Lot No.:	(b) (4)
Expiration[a]:	04 Oct 2023
Physical Description:	Light Brown Granule
Percentage of active compound:	61.34% of L-tryptophan
Correction Factor:	None
Density:	-
Storage Conditions:	Controlled room temperature between +15°C and +25°C, protected from light and humidity
Provided by:	Sponsor

- = Not applicable.

[a] In the case that the Study Sponsor has updated information (e.g., retest or stability data) that could affect the validity of the study, during or after its completion, then the Study Director should be informed.

5.3. Vehicle Control Identification

Vehicle Control Identification

	Vehicle Control
Identification:	Purified Water
Batch/Lot No.:	Details will be documented in the raw data and specified in the Study Report
Expiration/Retest Date:	
Storage Conditions:	Ambient or room temperature
Provided by:	Test Facility

5.4. Reserve Samples

For each batch (lot) of test item(s), a reserve sample will be collected and maintained under the appropriate storage conditions by the Test Facility.

5.5. Test and Control Material Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of the test item will be maintained. All unused Sponsor-supplied bulk test item, with the exception of reserve samples, will be returned to the Sponsor following issuance of the Draft Report unless otherwise requested (documentation will be retained in the study record). An earlier shipment of these materials may also be requested and authorized by the Study Director and Sponsor. See shipment of samples and study documentation for shipping details.

5.6. Safety

The following safety instructions apply to this study:

Standard laboratory handling precautions.

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6. DOSE FORMULATION AND ANALYSIS

6.1. Preparation of Formulations

Dose formulations will be divided into aliquots where required to allow them to be dispensed on each dosing occasion.

Dose Formulation	Administration Dose Form	Frequency of Preparation	Storage Conditions
Vehicle Control item	Solution	Not applicable (Commercial vehicle)	Room or ambient temperature
Test item	Suspension	Weekly	Immediately dispensed at room or ambient temperature

Any residual volumes from each dosing occasion will be discarded unless otherwise requested by the Study Director.

Stability of dose formulations: Stability analyses performed previously in conjunction with Test Site Study No. 21/300-316AN demonstrated that the test item formulation is stable when prepared and stored under the same conditions as those used in the present study, as follows:

- In a concentration range of 10-250 mg/mL for 8 days at room temperature and for 6 weeks at +4°C and -20°C. During the stability analysis, only the stability of the active ingredient (L-tryptophan in 61.34%) was examined. Therefore, there is no information about the stability of the other components in the test item.

Stability data have been retained in the study records of Test Site Study No. 21/300-316AN.

6.2. Preparation Details

The test item will be formulated in the selected vehicle (purified water) at the appropriate concentrations according to the Test Facility's SOPs and the dose levels selected in the study. The formulations will be stirred with magnetic stirrer from the preparation until completion of each treatment (except during transfer to the animal facility).

6.3. Sample Collection and Analysis

Dose formulation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

Appendix 1

Dose Formulation Sample Collection Schedule

Sample Type	Concentrations	Stratum	Sampling From	Number of Samples per Concentration			Sample Volume (mL/g)[b]	Intervals[c]
				Collected	Analyzed	Back up		
Concentration analyses	Groups 1 and 3	Middle	Preparation vessel	5	2	3	1	Day 1
Concentration / Homogeneity[a] analyses	Groups 2 and 4	Top		5	2	3	1	Day 1
		Middle		5	2	3	1	
		Bottom		5	2	3	1	
Concentration analyses	All groups	Middle		5	2	3	1	Week 13 (Sampled right after the last preparation)
		Middle		5	2	3	1	Week 13 (Sampled 8 days after the last preparation, under constant stirring)

[a] The averaged result from homogeneity analysis will serve as concentration verification.
[b] Sample size: 1 mL for solutions, 1 g for suspensions.
[c] When appropriate, samples will be collected from the formulation (bulk formulation if formulations are not prepared daily) to be used on the day of TK evaluation.

All samples to be analyzed will be stored at -20°C at the Test Facility before shipment to the Test Site for analysis, see Attachment B.

The analytical laboratory will be notified of the shipment of samples. Upon receipt at the analytical laboratory, the samples will be stored at -20°C.

6.3.1. Analytical Method

Analyses described below will be performed using a validated HPLC-UV (High Performance Liquid Chromatography with UV detection) analytical method (Test Site Study No. 21/300-316AN). During the analysis, the active ingredient (L-tryptophan) will be analysed directly. The concentration of the test formulations will be quantified based on its active ingredient content.

6.3.2. Formulation Analysis

Sample Allocation:	2 for analysis, 3 for backup (may be analyzed at the discretion of the Study Director).
Storage Conditions:	Within Stability Data.
Acceptance Criteria:	Concentration: Mean sample concentration results within or equal to ± 15% of theoretical concentration.

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Homogeneity: Relative Standard Deviation (RSD) of concentrations of ≤ 10% for each group.

7. TEST SYSTEM

Species/Species Family:	Rat.
Strain/Breed:	Wistar Han IGS.
Substrain:	Crl:WI(Han).
Animal Condition:	Naive.
Animal Procurement Method:	Purchased.
Animal Supplier:	(b) (4).
Animal Supplier Location:	(b)(6)
Number of Males:	50.
Number of Females:	50.

6 alternate animals (3 males and 3 females) will be purchased. If not used in this study, they will be held at the Test Facility.

Age at the Initiation of Dosing:	Approximately 6 weeks.
Weight at the Initiation of Dosing:	120 g to 330 g (males)/110 g to 260 g (females).

The actual age and weight of the animals at the initiation of dosing will be listed in the Final Report.

7.1. Animal Identification

Method: Subcutaneously implanted electronic identification chip.

7.2. Environmental Acclimation

Acclimation Period: Animals will be acclimatized to the study housing conditions for at least 7 days before the start of dosing.

7.3. Selection, Assignment, Replacement and Disposition of Animals

Selection/Assignment: Animals will be randomly assigned to groups at receipt. **The randomization should results in comparable mean body weight values among the groups (i.e., ± 20% of the mean). Main animals might be replaced by spare animals and/or invert between groups to meet the acceptance criteria.**

Replacement:	Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions. After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-test item-related health issues, or similar circumstances. The alternate animals may be used as replacements on the study within 7 days.
Disposition:	The disposition of all animals will be documented in the study records.

8. HUSBANDRY

8.1. Housing

Housing:	Group housed (up to 5 animals of the same sex and same dosing group together).
Caging:	Plastic cages containing appropriate bedding.
Cage Identification:	Color-coded cage card indicating study, group, animal number(s), and sex.

Animals will be separated during designated procedures/activities or will be separated as required for monitoring and/or health purposes, as deemed appropriate by Study Director and/or Clinical Veterinarian. Cages will be arranged on the racks in group order. Where possible, control group animals will be housed on a separate rack from the test item-treated animals.

For the recovery period (treatment-free period), animals may be housed in a room housing recovery animal of the same species from other study(ies), as per the Test Facility SOP.

8.2. Animal Enrichment

Animals will be socially housed for psychological/environmental enrichment and provide with items such as a small amount (handful) of shredded paper in each cage.

It is considered that there are no known contaminants in the enrichment that could interfere with the outcome of the study.

8.3. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	19°C to 25°C.
Humidity:	≥ 35%.
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures).
Ventilation:	10 or more air changes per hour.

8.4. Food

Diet:	Complete rodent diet (Reference No. A04C-12).
Type:	Pellets (alternate diet may be provided on an individual animal basis as approved by the Study Director).
Frequency/Ration:	*Ad libitum*, except during designated procedures.
Analysis:	Diet is sterilised by irradiation and analyzed by the supplier. Each batch of diet is supplied with a certificate of analysis which is verified and authorized for release by a veterinarian, and kept on file at the Test Facility. It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

8.5. Water

Type:	Municipal tap water, softened and filtered (0.2 µm) mains drinking water.
Frequency/Ration:	Freely available to each animal via an automatic watering system (except during designated procedures). Water bottles can be provided, if required.
Analysis:	Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility. It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

8.6. Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. In the event that animals show signs of illness or distress, the Responsible Veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director. If the condition of the animal(s) warrants therapeutic intervention or alterations in study procedures, the Sponsor Representative will be contacted, when possible, to discuss appropriate action(s). If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or Attending Veterinarian will attempt to consult with the Sponsor Representative prior to responding to the medical crisis, but the Study Director and/or Veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor Representative will be fully informed of any such events.

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9. EXPERIMENTAL DESIGN

Main and Recovery Animals

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume[a] (mL/kg)	Dose Concentration (mg/mL)	Number of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Vehicle control	0	10	0	10	10	5	5
2	Test item	500	10	50	10	10	-	-
3	Test item	1000	10	100	10	10	-	-
4	Test item	2000	10	200	10	10	5	5

- = Not applicable.
[a] Based on the most recent body weight measurement.

9.1. Administration of the Test and Control Materials

Route of Administration: Oral (gavage).

Treatment Frequency: Daily.

Treatment Duration: At least 90 days.

Method: The first day of dosing will be designated as Day 1. The dose formulations will be stirred at receipt and continuously during dosing. The doses will be given by gavage using a syringe with attached cannula.

10. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below will be performed for all main and recovery study animals.

General In-Life Assessments - Main and Recovery Study Animals

Parameter	Population(s)	Frequency (Minimum Required)	Comments
Mortality	All main study and recovery animals	At least twice daily[a] (morning and end of the working day) beginning upon arrival through termination/release	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings
Cageside Observations	All main study and recovery animals	Before and at least once after dosing on dosing days. At least once daily on non-dosing days, from at least Week -1[b]	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings
Detailed Clinical Observations	All main study and recovery animals	Weekly; from at least Week -1 and throughout the study	Animals are removed from the cage
Arena Observations	All main study and recovery animals	Once before the first administration of the test item and at least weekly thereafter	Animals will be observed for specific clinical signs in a standard arena

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Parameter	Population(s)	Frequency (Minimum Required)	Comments
Individual Body Weights	All main study and recovery animals	Weekly from at least Week -1 and throughout the study Animals may be weighed more often if necessary in order to monitor the health status	Last body weight before terminal fasting Not collected from animals found dead
Food Consumption	All main study and recovery animals	Weekly for each cage of animals from Day 1 and throughout the study	Quantitatively measured
Behavioral Functional Observational Battery (FOB)	5 main animals/sex/group Examination of Recovery animals (at the end of the recovery period) if findings at Week 13, (at additional cost)	On a suitable day during Week 13, before dosing	As detailed in the section below
Locomotor Activity Test (motor monitor test)			
Ophthalmology	All main and recovery study animals (including alternate animals pretest) Examination of Recovery animals (at the end of the recovery period) if findings at Week 13, at additional cost)	Once pretest (all animals) At the end of the dosing period (Week 13 - Groups 1 and 4 main study animals only)	See details in the section below
Estrous Cycle	All main study and recovery females	On the day of scheduled necropsy	See details in the section below

[a] Except on days of receipt and necropsy where frequency will be at least once daily.
[b] For observations that cannot be attributed to an individual animal due to social housing, the observation will be noted to each animal in the socialized group.

10.1. Behavioral Functional Observational Battery (FOB)

Behavorial tests will be conducted in group-housed animals.

FOB parameters will be evaluated per Test Facility SOPs and study-specific procedures (if any) as follows:

FOB Measurements

Functional Domains/ Parameters	Assessment Occasion			Type of Data	Rating Scale or Unit of Measurement
	Home Cage	During Handling	Open Field		
Activity Domain					
Arousal/Alertness	-	-	X	Categorical	-2 to 2
Posture/Body carriage	X	-	-	Categorical	-2 to 0
Stereotypy	X	-	X	Categorical	0 to 4

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Functional Domains/ Parameters	Assessment Occasion			Type of Data	Rating Scale or Unit of Measurement
	Home Cage	During Handling	Open Field		
Rearing	-	-	X	Counts	Counts
Appearance	-	-	X	Categorical	0 to 2
Excitability Domain					
Vocalizations	-	-	X	Categorical	0 to 1
Startle response	-	-	X	Categorical	-1 to 1
Ease of removal	-	X	-	Categorical	-1 to 2
Handling reactivity	-	X	-	Categorical	-1 to 2
Convulsions	X	-	X	Categorical	0 to 4
Autonomic Domain					
Exophthalmos	-	-	X	Categorical	0 to 1
Lacrimation	-	-	X	Categorical	0 to 2
Erected fur (piloerection)	-	-	X	Categorical	0 to 1
Pupil response	-	-	X	Categorical	0 to 2
Salivation	-	-	X	Categorical	0 to 2
Defecation	-	-	X	Categorical	-1 to 1
Palpebral closure/Ptosis	X	-	X	Categorical	0 to 2
Neuromuscular Domain					
Gait/Mobility	-	-	X	Categorical	0 to 3
Grip strength (forelimbs)	-	-	X	Continuous	Grams
Grip strength (hindlimbs)	-	-	X	Continuous	Grams
Air righting reflex	-	-	X	Categorical	0 to 2
Tremor	X	-	X	Categorical	0 to 3
Body tone	-	-	X	Categorical	-1 to 1
Sensorimotor Domain					
Touch response/Tactile reflex	-	-	X	Categorical	-1 to 1
Tail pinch response	-	-	X	Categorical	-1 to 1
Physiological Domain					
Respiration	-	-	X	Categorical	-1 to 2
Body temperature	-	-	X	Continuous	Degree Celsius

A detailed description of the measurements/scoring performed during the FOB will be presented in the Study Report. Any other clinical and/or behavioral abnormalities will also be noted and presented in the Study Report.

In a first step, the animal will undergo neurobehavioral evaluation in the home cage with ranking of posture, palpebral closure, stereotypies, convulsions, and tremors.

In a second step, the ease of removal of the animal from the home cage and its reactivity to handling during removal and transfer to the open field will be scored.

In a third step, the animal will be placed in a 50 x 50 x 20 cm black open field and observed for 2 minutes in freely moving conditions. Arousal, vocalizations, respiration, gait, stereotypies, convulsions and tremors will be ranked. The number of rearing occasions will be counted.

At the end of the 2-minute observation period, defecation (aspect of feces) will be ranked and the animals will undergo a series of additional observations and tests (from the least to the most invasive).

- The observer will handle the animals and rank fur appearance, lacrimation, salivation, exophthalmos, palpebral closure, and erected fur (piloerection).
- The animal will be tested for various reflexes such as response to a touch of the body with a rod, startle response (using a clicker), tail pinch response and pupil response.
- Body temperature will be measured using a rectal probe.
- The animal will be ranked for body tone, forelimbs and hindlimbs grip strength and air righting reflex (from a height of 30 cm). Forelimbs and hindlimbs grip strength will be measured with a T-shaped bar connected to a dynamometer that determines the maximal force developed by the limbs when the operator pulls the animal away from the bar. The measure will be performed 3 times (individual values of repeated measurements kept in the raw data but not reported) and the mean value will be calculated and reported.

10.2. Locomotor activity test

A locomotor activity test will be performed in an open field in order to assess reactivity to a novel environment and motor activity. Activity will be monitored by a photobeam analysis system (Motor Monitor supplied by (b) (4)) for 1 hour. The arena is divided by 7 and 15 equally spaced infrared beams in width and length, respectively; the time and the number of beams interrupted by the animal will be recorded. Motor activity is divided into 2 types of activity: Ambulatory activity (large animal movements like walking) and fine movements (including grooming and head movements). The proportion of beams blocked by the rat in each type of activity will be calculated.

10.3. Ophthalmic examinations

Animals: Additional examination of Groups 2 and 3 at the end of the dosing period and/or of recovery animals at the end of the recovery period will be conducted only if considered necessary to further investigate initial findings (to be confirmed by Study Plan amendment- at additional cost).

Procedure: A mydriatic agent (Tropicamide) will be instilled into the eyes before examination. Examination of adnexa, optic media and fundus will be performed by indirect ophthalmoscopy. An examination using a slit lamp may be performed if necessary to examine the anterior segment of the eye (including the lens).

Evaluation: The interpretation of results will be done by a Veterinary Ophthalmologist.

10.4. Estrous Cycles

On the day of scheduled necropsy, a vaginal smear will be taken to determine the cycle stage and allow correlation with histopathology of female reproductive organs. The vaginal smears performed before necropsy will be fixed with air-drying and ethanol. Once the cycle stage is determined, the vaginal smears will be stained with hematoxylin and eosin (see Section 13.1).

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11. CLINICAL PATHOLOGY

11.1. Sample Collection

Clinical Pathology Sample Collection

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	Hormone Analysis	Urinalysis
1 to 4 (main animals only)	Day 91 or Day 92	X	X	X	X[c]	X
1 and 4 (recovery animals only)	Day 120	X	X	X	X[c]	X
Unscheduled euthanasia[a] (when possible)	-	X	X	X	-	-
Fasting (overnight, about 16hr):		-	-	Yes	Yes	Yes
Method/Comments:		Submental vein sinus or sublingual vein under slight anesthesia (or other site as deemed necessary)				Deprived of food, and water ad libitum
Target Volume (mL)[b]:		0.5	0.9	1.0	1.3	As available
Anticoagulant:		EDTA-K_2	Trisodium citrate	None	None	-
Special Requirements:		-	-	-	**Samples to be kept at room temperature for at least 30 minutes to allow clotting (maximum up to 2 hours)**	-
Processing:		None	Plasma	Serum	Serum	-

X = Sample to be collected; - = Not applicable; hr = Hour.

[a] Order of priority to be defined if appropriate.

[b] Additional samples may be obtained (e.g., due to clotting of non-serum samples) if permissible sampling frequency and volume are not exceeded.

[c] **Between 7.00 and 10.30 a.m. because of diurnal variation of hormone levels.**

11.2. Hematology

Hematology Parameters

Red blood cell count	Platelet count
Hemoglobin concentration	Mean Platelet volume
Hematocrit	White blood cell count
Mean corpuscular volume	Neutrophil count
Red Blood Cell Distribution Width (gated)	Lymphocyte count
Mean corpuscular hemoglobin concentration	Monocyte count
Mean corpuscular hemoglobin	Eosinophil count
Mean Platelet Volume	Basophil count
Reticulocyte count	Large unstained cells count

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A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. Individual blood smears may be examined to confirm certain analyzer results, as required by SOP.

If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a Study Plan amendment.

Morphology findings that require confirmation, as required by SOP, will be reviewed by a clinical pathologist or designee at (b) (4).

11.3. Coagulation

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time

11.4. Clinical Chemistry

Clinical Chemistry Parameters

Alanine aminotransferase	Albumin
Aspartate aminotransferase	Globulin (calculated)
Alkaline phosphatase	Albumin/Globulin ratio
Total bilirubin[a]	Glucose
Urea nitrogen/Urea	Cholesterol
Creatinine	**High Density Lipoprotein**
Calcium	**Low Density Lipoprotein**
Phosphorus	Triglycerides
Bile acids	Sodium
Total protein	Potassium
Gamma glutamyl transferase	Chloride

[a] When total bilirubin is > 10 µmol/L, direct bilirubin will also be measured and indirect bilirubin will be calculated.

11.5. Urinalysis

Urinalysis Parameters

Volume[a]	Protein
Color	Glucose
Appearance/Clarity	Bilirubin
Specific gravity	Ketones
pH	Blood
Nitrite	**Osmolality**
	Sediment

11.6. Bone Marrow Smear Evaluation

Bone marrow smears will be collected as described in the terminal procedures table (see Attachment A) and will be staining using the Aerospray automaton (May-Grünwald Giemsa method).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the Pathologist and the Sponsor.

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11.7. Thyroid Hormone Analysis

11.7.1. Sample preparation

Sample preparation:

Centrifugation	Volume Serum Aliquot 1	Volume Serum Aliquot 2	Volume Serum Aliquot 3	Volume Serum Aliquot 4	Freezing	Specific Request
1800 g 10 minutes Approximately **+21°C**	(b) (4)					Samples to be kept at room temperature for at least (b minutes to) allow clotting (maximum up to 2 hours)

Theoretical number of serum samples: 100 samples x 4 aliquots.

The samples will be dispatched in dry ice with recording device to Test Site after the last sampling occasion (see Attachment B).

After reception at Test Site, the samples will be immediately analyzed or stored at (-80 ± 10 °C) until analysis.

11.7.2. Thyroid hormone analysis

Samples from all animals will be assessed for T3, T4 and TSH levels (Study Phase No. 21/300-430AN).

Levels of thyroid hormones will be determined using validated methods in compliance with relevant SOPs. Details will be given in the phase report.

Each assay will consist of:

- blank samples (will be documented in the raw data and reported in a phase report)
- calibration curve, calculated by at least five calibration levels
- QC samples (assayed in duplicate in case of TSH and in triplicate in case of T3 and T4 hormones, concentrations will be documented in the raw data and reported)
- study samples

Stability in rat serum: 132 days for T3 and T4, and 142 days for TSH when stored at a temperature set to maintain -80 ± 10 ºC.

11.7.3. Acceptance criteria

Back-calculated results of each calibration point should be within ± 25% of their nominal values, except of 0 level.

Results of QC samples should be within ± 25% of their nominal values and valid results should be accepted at least two out of three results for each QC level in case T3 and T4 measurements and at least one out of two results for each QC level in case of TSH.

Invalid runs will be automatically repeated. If re-assay of samples will be needed, the reason will be documented in the raw data and reported.

Appendix 1

In the case of concentration values above the highest validated level, samples will be diluted with the zero calibrator (will be documented and reported) to obtain a concentration within the validated range. If any dilution will be prepared, then it will be documented in the raw data and reported in the study report.

Any sample not required for analysis will be discarded following acceptance of the results of the hormone analysis by the Principal Investigator and Study Director after the finalization of the study report.

12. TERMINAL PROCEDURES

Terminal procedures are summarized in the following tables:

Main Study Animals

Group No.	Scheduled Euthanasia Day	Necropsy Procedures			Histology Processing	Microscopic Evaluation
		Necropsy	Tissue Collection	Organ Weights		
Found dead or unscheduled euthanasia	-	X	Full list[a]	-	Full list[a]	Full list[a]
1 and 4	91-92	X	Full list[a]	Full list[a]	Full list[a]	Full list[a]
2 and 3	91-92	X	Full list[a]	Full list[a]	Gross lesions Target tissues[b]	Gross lesions Target tissues[b]

X = Procedure to be conducted; - = Not applicable.

"Histology Processing": Embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

[a] See Attachment A for list of tissues applicable to each procedure.

[b] Any target tissues identified by the Study Pathologist during microscopic evaluation of full list animals will be communicated to the Study Director, then processed, evaluated and reported in non-full list animals.

Recovery Animals

Group No.	Scheduled Euthanasia Day	Necropsy Procedures			Histology Processing	Microscopic Evaluation
		Necropsy	Tissue Collection	Organ Weights		
Found dead or unscheduled euthanasia	-	X	Full list[a]	-	Full list[a]	Full list[a]
1 and 4	120	X	Full list[a]	Full list[a]	Gross lesions Target tissues[b]	Gross lesions Target tissues[b]

X = Procedure to be conducted; - = Not applicable.

"Histology Processing": Embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

[a] See Attachment A for list of tissues applicable to each procedure.

[b] Any target tissues identified by the Study Pathologist during microscopic evaluation of full list animals will be communicated to the Study Director, then processed, evaluated and reported in non-full list animals.

12.1. Method of Euthanasia

Animals will be euthanized by carbon dioxide inhalation followed by exsanguination or by isoflurane inhalation followed by exsanguination for unscheduled necropsy/blood sampling.

12.2. Unscheduled Euthanasia

Main study and recovery animals to be euthanized for humane reasons before the scheduled time will undergo a final clinical observation, and biological samples will be obtained if possible as specified in relevant sections.

12.3. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia will be fasted overnight before necropsy and will have a terminal body weight recorded. When applicable, the animals will be euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, will be necropsied throughout the day.

12.4. Necropsy

Animals as detailed in the terminal procedures table will be subjected to a complete necropsy examination, which will include evaluation of the carcass and musculoskeletal system, all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Images may be generated for illustration of or consultation on gross observations, at the discretion of the Study Pathologist and/or the Study Director. These images will not be used for data generation or interpretation and will not be archived or included in the Final Report.

Any remaining tissues not required for histopathology or retention may be harvested from the carcass of vehicle control animals before disposal. These tissues, if collected, may be used for validation or investigational purposes and as such are not part of this study and will not interfere with the study objectives.

12.5. Organ Weights

The organs detailed in the tissue table in Attachment A will be weighed at necropsy. Paired organs will be weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as an observation comment. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight will be calculated.

12.6. Tissue Collection and Preservation

Representative samples of tissues will be collected and preserved in 10% neutral buffered formalin, as detailed in the tissue table in Attachment A. Additional tissue samples may be collected to elucidate abnormal findings.

13. HISTOLOGY AND MICROSCOPIC EVALUATION

13.1. Histology

Tissues as detailed in the tissue table in Attachment A will be processed at the Test Facility.

The same sampling and trimming procedures will be used for all applicable tissues in all applicable dose groups.

Appendix 1

For the testicles of males from Groups 1 and 4 main animals, detailed qualitative examination will be made taking into account the tubular stages of the spermatogenic cycle. In addition to the haematoxylin and eosin-stained slide, an additional slide will be prepared and examined, stained with PAS. The examination will be conducted in order to identify treatment related effects such as missing germ cell layers or types, retained spermatids, multinucleate or apoptotic germ cells and sloughing of spermatogenic cells into the lumen. Any cell- or stage-specificity of testicular findings will be noted.
Vaginal smears performed before necropsy will be stained with hematoxylin and eosin after air-drying and ethanol fixation at the Test Facility.

Sperm analysis will be performed for Groups 1 to 4, using automated equipment ((b) (4) . The left cauda epididymis will be sampled and used for the assessment of caudal sperm reserves and sperm motility, including progressive motility. Sperm counts will be performed using the left testis following removal of the tunica albuginea. In the case of an abnormality of the left epididymis or testis, the right organs may be used for sperm analysis.

Sperm morphology will be evaluated for Groups 1 and 4, (at least 200 sperm per sample, where possible). The numbers of sperm with each type of abnormality will be recorded. Slides for assessment of sperm morphology will be prepared for all surviving males from all groups. Evaluation will be performed for the control and high dose groups in first instance. If a treatment-related effect is found, the intermediate dose groups will also be examined.

13.2. Microscopic Evaluation

Histopathological evaluation will be performed by a veterinary pathologist with training and experience in laboratory animal pathology.

Histopathological examination will be performed for all gross lesions from animals in all groups, except those for which the diagnosis is judged unnecessary for the outcome of the study by the Pathologist.

Special stains may be used at the discretion of the Pathologist to further characterize lesions and changes identified during routine evaluation of individual animals. Any special stains will be documented in the individual animal data. Any additional stains or evaluations, if deemed necessary by the Pathologist, may be added by Study Plan amendment following discussion with the Study Director and in consultation the Sponsor.

Efforts will be made to evaluate all Study Plan-required tissues microscopically; however, it is not always feasible for every Study Plan-required tissue to be present on every slide. Study Plan-required tissues that are not examined will be documented in the histopathology data and the impact of these missing tissues on the study will be documented in the Pathology Report.

Images may be generated for illustration of or consultation on histological observations. These images will not be used for data generation or interpretation and will not be archived or included in the Final Report.

13.3. Pathology Peer Review

A Pathology Peer Review will be conducted according to internal procedures by another Pathologist at the Test Facility. The Peer Review Statement or equivalent documentation will be included as an appendix to the Final Report or in the study file.

Any additional Peer Reviews of the histological sections will be documented in an amendment to this Study Plan (these may be at additional cost and may impact reporting dates).

14. STATISTICAL ANALYSIS

Any data collected during the predose period will be tabulated, summarized, or statistically analyzed. All statistical analyses will be performed within the respective study phase, unless otherwise noted. Numerical data collected on scheduled occasions will be summarized and statistically analyzed as indicated below according to sex and occasion.

14.1. Constructed Variables

Body Weight Changes:	Calculated between each scheduled interval.
Food Consumption:	Calculated between each scheduled interval (individual data only) and as specified above for bodyweight gains. Summarization and statistical analysis intervals will reflect the same intervals as the bodyweight gains. In case of any animal replacement, the statistical analysis of food consumption data cannot be performed due to data acquisition system constraints.
Organ Weight Relative to Body Weight:	Calculated against the terminal body weight for scheduled intervals.
Organ Weight Relative to Brain Weight:	Calculated against the brain weight for scheduled intervals.

Additional or alternative body weight or food consumption intervals may be evaluated to elucidate study results at the discretion of the Study Director.

14.2. Descriptive Statistical Analyses

Means, standard deviations (or % coefficient of variation or standard error, when deemed appropriate), ratio, percentages, numbers, and/or incidences will be reported as appropriate by dataset.

14.3. Inferential Statistical Methods

All statistical tests will be conducted at the 5% significance level. All pairwise comparisons will be conducted using two-sided tests and will be reported at the 1% and 5% levels, unless otherwise noted.

Appendix 1

The pairwise comparisons of interest are listed below:

Group 2	vs.	Group 1
Group 3	vs.	Group 1
Group 4	vs.	Group 1

Analyses will be performed according to the matrix below when possible, but will exclude any group with less than 3 observations.

Statistical Matrix

Variables for Inferential Analysis	Statistical Method		
	Parametric/ Non-Parametric	Non-Parametric	Incidence
Body weight	X	-	-
Body weight gains	X	-	-
Food consumption	X	-	-
Hematology variables	X	-	-
Coagulation variables	X	-	-
Clinical chemistry variables	X	-	-
Urinalysis variables	X	-	-
Thyroid hormones[a]	X	-	-
FOB qualitative variables	-	-	-
FOB quantitative variables	X	-	-
(b) (4) Monitor	X	-	-
Organ weights	X	-	-
Organ weight relative to body weight	X	-	-
Organ weight relative to brain weight	X	-	-
Sperm morphology	-	X	-
Sperm count and motility	X	-	-

X = Statistical analysis performed.
- = Statistical analysis not performed.
[a] Analysis to be performed at the Test Site.

14.4. Parametric/Non-Parametric

Levene's test will be used to assess the homogeneity of group variances.

The groups will be compared using an overall one-way ANOVA F-test if Levene's test is not significant or the Kruskal-Wallis test if it is significant. If the overall F-test or Kruskal-Wallis test is found to be significant, then pairwise comparisons will be conducted using Dunnett's or Dunn's test, respectively.

14.5. Non-Parametric

The groups will be compared using an overall Kruskal-Wallis test. If the overall Kruskal-Wallis test is found to be significant, then the above pairwise comparisons will be conducted using Dunn's test.

For datasets intended to include only two groups, the two groups will be compared using a Dunn's test.

14.6. For Data Generated Outside (b) (4)

Sperm count, (b) (4) Monitor and motility data will be analysed using a (b) (4) software package. Levene's test will be used to test the equality of variance across groups and Shapiro-Wilk's test will be used to assess the normality of the data distribution in each group. Data with homogeneous variances and normal distribution in all groups will be analysed using ANOVA followed by Dunnett's test. Data showing non-homogeneous variances or a non-normal distribution in at least 1 group will be analysed using Kruskal-Wallis test followed by the Wilcoxon's rank sum test.

For datasets intended to include only two groups, Levene's test will be used to test the equality of variance across groups and Shapiro Wilk's test will be used to assess the normality of the data distribution in each group. Data with homogeneous variances and normal distribution in all groups will be analysed using the Student's t-test. Data showing non-homogeneous variances or a non-normal distribution in at least 1 group will be analysed using the Wilcoxon's rank sum test.

15. COMPUTERIZED SYSTEMS

The following computerized systems may be used in the study. The actual computerized systems will be documented in the Final Report.

Computerized Systems

System Name	Description of Data Collected and/or Analyzed
(b) (4)	Environmental Monitoring System
(b) (4)	Test item receipt, accountability and/or formulation activities; in-life; clinical pathology; postmortem; statistical analysis
(b) (4)	Safety Assessment document management and publishing Collection of 21 CFR Part 11 compliant signature
(b) (4)	Electronic Signature
	Deviation information library
	Statistical Analysis
	Locomotor activity test
	Sperm Analyser
	Hematology Parameters (interfaced to (b) (4)
	Coagulation Parameters (interfaced to
	Coagulation Parameters (interfaced to
	Biochemistry Parameters (interfaced to
	Urine Parameters (interfaced to (b) (4)
	Sample tracking
	System control, data acquisition and integration

(b) (4) (version 2003 or higher) may be employed to present certain results and d calculations.

Data for parameters not required by the Study Plan, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by the Study Plan and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

16. REGULATORY COMPLIANCE

The study will be performed in accordance with OECD Principles of Good Laboratory Practice as required in Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004, Good Laboratory Practices in Article Annexe II de l'article D523-8 du code de l'environnement du 16 octobre 2007.

If applicable, the regulatory compliance to applicable regulations of electronic signature system developed and used by the Sponsor is under his responsibility.

OECD Principles of Good Laboratory Practice are accepted by Regulatory Authorities throughout the European Union, United States of America (FDA and EPA) and Japan (MHLW, MAFF and METI) and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

In order to enable the results of the study phases conducted in Hungary to meet the requirements for regulatory submission and/or safety assessment, the study will be performed in compliance with the principles of Good Laboratory Practice Regulations as requested by the Sponsor and specified in the Hungarian Good Laboratory Practice Regulations of 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities. Those regulations correspond to the OECD Principles of Good Laboratory Practice (OECD GLP, ENV/MC/CHEM (98) 17) and as accepted by Regulatory Authorities throughout the European Union, United States of America, Japan, and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

17. QUALITY ASSURANCE

17.1. Test Facility

The Test Facility Quality Assurance Unit (QAU) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAU will review the Study Plan (and any amendments), conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to assure that it accurately describes the methods and Standard Operating Procedures and that the reported results accurately reflect the raw data of the study.

All Quality Assurance documents will be retained by the Test Facility as their property and will not be returned to the Study Sponsor.

17.2. Test Site(s)

For all study phases inspected by Test Site QAU(s), copies of each inspection report will be made available to the Study Director, Test Facility Management, and the Test Facility Lead QA.

18. AMENDMENT(S) AND DEVIATIONS

Changes to the approved Study Plan shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary Study Plan changes in advance with the Sponsor.

Appendix 1

All Study Plan and SOP deviations will be documented in the study records. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

Deviations from the Study Plan and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the Principal Investigator, and reported to the Study Director for authorization/acknowledgement.

19. RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, Study Plan, retained samples and specimens, and the Final Report will be archived at the Final Report issue. All materials generated by (b) (4) from this study will be transferred to a (b) (4) archive and kept for a period of 15 years following the date of issue of the Final Report.

Disposition of residual/retained analytical samples will be as described in the table below.

Disposition of Residual/Retained Samples

Sample Type	Disposition	Schedule
Analytical (and test item used in analysis)	Discard residual volumes	Samples will be maintained for the defined period of stability, and then discarded
Thyroid hormones	Discard residual volumes	Samples will be maintained for a maximum of 6 months following issuance of the first full Draft Report after which samples will be managed as defined in the 'disposition' column as requested and authorized by the Study Director and in consultation with the Sponsor

Records to be maintained will include, but will not be limited to, documentation and data for the following:

- Deviations, Study Plan amendments and Study Plan.
- Study schedule.
- Study-related correspondence.
- Test system receipt, health, and husbandry.
- Test materials receipt, identification and preparation.
- Reserve sample.
- In-life measurements and observations.
- Clinical pathology sample collection and evaluation.
- Hormone samples collection and analysis.
- Gross and microscopic observations and related data.
- Organ weight measurements.
- Statistical analysis results.
- Original signed Final Report.

Original Study Plan and amendment(s) signed by the Sponsor (wet signature or e-signed documents) will be maintained either at (b) (4) or archived at the Sponsor under his responsibility and should be made available in case of monitoring authority request.

The disposition of the original documents signed by the Sponsor will be described in the Study Report.

20. STUDY CLASSIFICATION

Submission Study Category:	Toxicology.
Submission Study Type:	Repeat dose toxicity.
Study Design:	Parallel.
Primary Treatment CAS Registry No.:	73-22-3.

21. REPORTING

The Study Sponsor will be informed promptly of any significant findings at any time during the study.

A Draft Report with extended methods will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft and Final Report(s), provided in Adobe Acrobat PDF format (hyperlinked and searchable at final), along with a Microsoft Word version of the text. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Test Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation.

22. JUSTIFICATION AND GUIDELINES

22.1. Justification of Test System and Number of Animals

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models which do not use live animals currently do not exist.

The rat was chosen as the animal model for this study as it is an accepted rodent species for toxicity testing by regulatory agencies.

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the test item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

22.2. Justification of Route and Dose Levels

The oral route of administration was selected because this is the route of administration specified in the OECD 408 and OCSPP guidelines. The dose levels were set by the Study Director in agreement with the Study Monitor based on the available information of the chemical nature, characteristics of the test item, and available data and information from previous experimental work, including the results of a Dose Range Finding (DRF) study

(Study code 21/300-101PE). Based on those results where the test item was given at 500, 1000 and 2000 mg/kg bw in distilled water, 2000 mg/kg bw/day was selected as the High dose for this study. The low and intermediate dose levels of 500 and 1000 mg/kg/day were selected to derive a dose-response for any effects that may be observed.

22.3. Guidelines for Study Design

The design of this study was based on the study objective(s), the overall product development strategy for the test item, and the following study design guidelines:

- OECD Guideline 408 (2018). Repeated Dose 90-day Oral Toxicity Study in Rodents.
- EPA Health Effects Test Guideline OPPTS 870.3100: 90-Day Oral Toxicity in Rodents.

23. ANIMAL WELFARE

The study design was reviewed and approved by the ethical committee of the Test Facility as per the Standard Project Authorization No. (b) (4).

The study design, animal housing and associated procedures are in general compliance with the following animal health and welfare guidelines:

- Guide for the care and use of laboratory animals, 2011.
- Decree No. 2013-118 relating to the protection of animals used in scientific experiments described in the Journal Officiel de la République Française on 01 February 2013.
- Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

The Test Facility is AAALAC accredited.

By approving this Study Plan, the Sponsor affirms that there were no other alternative experimental methods other than the use of live animals to achieve the required objectives, that the harm-benefit analysis of the project was performed and that this study does not unnecessarily duplicate any previous experiments.

Appendix 1

ATTACHMENT A

Tissue Weighing, Collection, Processing and Evaluation Table

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Animal ID	-	X	-	-
Artery, aorta	-	X	X	X
Body cavity, nasal	-	X	-	-
Bone marrow, sternum	-	X	X	X
Bone marrow smear	-	X[a]	-	-
Bone, femur	-	X (1)	X (1)	X (1)
Bone, sternum	-	X	X	X
Brain	X	X	X	X
Epididymis[e]	X (2)	X (2)[b]	X (2)	X (2)
Esophagus	-	X	X	X
Eye	-	X (2)[b]	X (2)	X (2)
Ganglion, dorsal root, lumbar	-	X	-	-
Gland, adrenal	X (2)	X (2)	X (2)	X (2)
Gland, clitoral	-	X (2)	-	-
Gland, lacrimal	-	X (2) (extra-orbital)	-	-
Gland, Harderian	-	X (2)	X (1)	X (1)
Gland, mammary	-	X	X	X
Gland, parathyroid	-[d]	X (2)	X (2)	X (2)
Gland, pituitary	X	X	X	X
Gland, preputial	-	X (2)	-	-
Gland, prostate	X	X	X	X
Gland, salivary, submandibular	-	X (2)	X (1)	X (1)
Gland, salivary, sublingual	-	X (2)	-	-
Gland salivary, parotid	-	X (2)	-	-
Gland, seminal vesicle **with coagulating gland**	X (2)	X (2)	X (2)	X (2)
Gland, thyroid	X (2)	X (2)	X (2)	X (2)
Gland, Zymbal's	-	X (2)	-	-
Gut-associated lymphoid tissue[c]	-	X	X	X
Heart	X	X	X	X
Joint, femorotibial	-	X (1)	X (1)	X (1)
Kidney	X (2)	X (2)	X (2)	X (2)
Large intestine, cecum	-	X	X	X
Large intestine, colon	-	X	X	X
Large intestine, rectum	-	X	X	X
Larynx	-	X	-	-
Liver	X	X	X	X
Lung	-	X	X	X
Lymph node, mandibular	-	X (2)	X (1)	X (1)
Lymph node, mesenteric	-	X	X	X
Macroscopic abnormalities	-	X	X	X
Muscle, skeletal	-	X (2)	X (1)	X (1)
Nerve, optic	-	X (2)[b]	X (2)	X (2)
Nerve, sciatic	-	X (2)	X (1)	X (1)
Nerve, tibial	-	X (2)	-	-
Ovary	X (2)	X (2)	X (2)	X (2)

Appendix 1

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Olfactory bulbs	-	X	X	X
Oviduct	-	X (2)	-	-
Pancreas	-	X	X	X
Skin	-	X	X	X
Small intestine, duodenum	-	X	X	X
Small intestine, ileum	-	X	X	X
Small intestine, jejunum	-	X	X	X
Spinal cord	-	X	X	X
Spleen	X	X	X	X
Stomach	-	X	X	X
Testis[e]	X (2)	X (2)[b]	X (1)	X (1)
Thymus	X	X	X	X
Tongue	-	X	X	X
Trachea	-	X	X	X
Ureter	-	X (2)	-	-
Urinary bladder	-	X	X	X
Uterus/Cervix	X	X	X	X
Vagina	-	X	X	X
Vaginal smear	-	X	X	-

X = Procedure to be conducted; - = Not applicable; (1) = One side; (2) = Both sides.

Macroscopic abnormalities in the organs listed and in other organs will be sampled at necropsy, processed for histology and examined microscopically.

[a] 2 bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry.

[b] Eyes and optic nerves are preserved in Davidson's fixative. Testes and epididymides are preserved in modified Davidson's fixative.

[c] From small intestine: Peyer's patch or solitary lymphoid follicle.

[d] Weigh with gland, thyroid.

[e] For terminal and recovery males from groups 1 and 4 (except any premature decedent), the left testis and epididymide will be dedicated for sperm analysis, the right organs for the histopathological examination. Both testes and epididymides will be weighed (separately) as well as the left cauda of the epididymide dedicated for sperm analysis. After analysis of sperm, the remainder of the left epididymide could be preserved.

Appendix 1

ATTACHMENT B

Shipment of Samples and Study Records

Matrix	Purpose	Day/ Week/ Aliquot	Proposed Shipment Date	Conditions for Shipment	Recipient/Address
Formulations	Dose Formulation Analysis	Day 1 (2 first aliquots)	19 Oct 2022	Dry Ice	(b) (4), (b)(6)
		Week 13 – 2 occasions (2 first aliquots)	21 Jan 2023	Dry Ice	
Serum	Thyroid Hormone Analysis	All	15 Feb 2023	Dry ice	

Appendix 1

SPONSOR AMENDMENT APPROVAL

The signature of the Sponsor Representative below indicates approval of this document.

DocuSigned by:
(b)(6)

Sponsor Representative

Appendix 1

TEST FACILITY AMENDMENT APPROVAL

All electronic signatures appear at the end of the document upon finalization.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 1

SIGNATURE(S) FOR DOCUMENT: (b) (4) - Study Plan Amendment 04

TFM Approval: I approve this document.

Name: (b)(6)

Electronically Signed in (b) (4) — 06-Feb-2023 06:59:22 (UTC+00:00) Timestamp

Study Director Approval: I approve this document.

Name: (b)(6)

Electronically Signed in (b) (4) — 06-Feb-2023 08:05:11 (UTC+00:00) Timestamp

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 1

(b) (4)

FINAL STUDY PLAN

Test Facility Study No. (b) (4)

Sponsor Reference No. (b) (4)

90-Day Repeated Dose Toxicity Study of TRP Pro by the Oral (gavage) Route in the Wistar Han IGS Rat With a 4-Week Recovery Period

(b) (4) Study

SPONSOR:
CJ CheilJedang Corporation
55-42 Beongil Gwanggyo-ro, Yeongtong-gu
Suwon-si
16495 Gyeonggi-do
Republic of Korea

TEST FACILITY:
(b) (4)

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Appendix 1

1. OBJECTIVE(S)

The objective of this study is to determine the potential toxicity of TRP Pro when given by the oral (gavage) route for 90 days to the Wistar Han IGS rat and to evaluate the potential reversibility of any findings after a 4-week recovery period.

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual dates will be included in the Final Report.

Animal Arrival:	10 Oct 2022.
Experimental Starting Date:	10 Oct 2022.
Initiation of Dosing:	18 Oct 2022.
Completion of In-Life:	End of Dosing Period: 16 and 17 Jan 2023. End of Recovery Period: 14 Feb 2023.
Experimental Completion Date:	03 Oct 2023. (last date on which data are collected).
Data Review Meeting:	Week of 24 Apr 2023.
Draft Report:	09 May 2023.
Consolidated Sponsor Comments:	09 Jun 2023.
Unsigned Final Report:	03 Oct 2023. This date is dependent on the date of receipt of Sponsor comments and final contributing Phase Reports. Any delay may have repercussions on the issue date of the Final Draft Report.
Final Report:	24 Oct 2023 (expected date of Study Director signature of report).

The contributions from Principal Investigators to Study Director are proposed at the dates indicated below to allow inclusion in the Draft Study Report.

Dose Formulation Analysis Draft Report:	07 Apr 2023.
Dose Formulation Analysis Final Report:	01 Sep 2023.
Thyroid Hormone Analysis Draft Report:	07 Apr 2023.
Thyroid Hormone Analysis Final Report:	01 Sep 2023.

Appendix 1

3. SPONSOR

Role	Name	Contact Information
Sponsor Study Monitor/Representative Name	(b) (4)	Address as cited for Sponsor Tel: +82 31 8099 1548 E-mail: (b) (4)@cj.net

4. RESPONSIBLE PERSONNEL

Role/Phase	Quality Assurance Unit	Name	Contact Information
Study Director	(b) (4), (b)(6)		
Alternative Contact			
Test Facility Management			
Test Facility Lead QA			
Individual Scientist (IS)			
Ophthalmology	(b) (4), (b)(6)		
Safety Pharmacologist			
Study Pathologist			
Principal Investigators (PI)			
Formulation Analysis (Phase No. 21/300-420AN)[a]	(b) (4), (b)(6)		
T3, T4, TSH hormone measurement (Phase No. 21/300-430AN)[a]			

Appendix 1

Role/Phase	Quality Assurance Unit	Name	Contact Information
Test Site QAU			(b) (4), (b)(6)

[a] Test Site selected by the Study Director in agreement with the Study Sponsor.

Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner for authorization/acknowledgement. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report.

The Phase Report will include the following:

- A statement of compliance.
- A QA statement.
- The archive site for all records, samples, specimens, and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report).
- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase.

5. TEST MATERIALS

5.1. Test Material Characterization

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity, composition, and stability for the test item(s) provided. A certificate of analysis or equivalent documentation will be provided for inclusion in the Final Report. The Sponsor will also provide information concerning the regulatory standard (GLP, GMP, or other) followed for these evaluations.

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the test item(s) provided, and this information is available to the appropriate regulatory agencies should it be requested.

Appendix 1

5.2. Test Material Identification

Test Item Identification

	Test Item
Identification:	TRP Pro
Alternate identification	L-tryptophan (TRP Pro)
Batch/Lot No.:	(b) (4)
Expiration[a]:	04 Oct 2023
Physical Description:	Light Brown Granule
Percentage of active compound:	61.34%
Correction Factor:	None
Density:	-
Storage Conditions:	Controlled room temperature between +15°C and +25°C, protected from light and humidity
Provided by:	Sponsor

- = Not applicable.

[a] In the case that the Study Sponsor has updated information (e.g., retest or stability data) that could affect the validity of the study, during or after its completion, then the Study Director should be informed.

5.3. Vehicle Control Identification

Vehicle Control Identification

	Vehicle Control
Identification:	Purified Water
Batch/Lot No.:	Details will be documented in the raw data and specified in the Study Report
Expiration/Retest Date:	
Storage Conditions:	Ambient or room temperature
Provided by:	Test Facility

5.4. Reserve Samples

For each batch (lot) of test item(s), a reserve sample will be collected and maintained under the appropriate storage conditions by the Test Facility.

5.5. Test and Control Material Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of the test item will be maintained. All unused Sponsor-supplied bulk test item, with the exception of reserve samples, will be returned to the Sponsor following issuance of the Draft Report unless otherwise requested (documentation will be retained in the study record). An earlier shipment of these materials may also be requested and authorized by the Study Director and Sponsor. See shipment of samples and study documentation for shipping details.

5.6. Safety

The following safety instructions apply to this study:

Standard laboratory handling precautions.

6. DOSE FORMULATION AND ANALYSIS

6.1. Preparation of Formulations

Dose formulations will be divided into aliquots where required to allow them to be dispensed on each dosing occasion.

Appendix 1

Dose Formulation	Administration Dose Form	Frequency of Preparation	Storage Conditions
Vehicle Control item	Solution	Not applicable (Commercial vehicle)	Room or ambient temperature
Test item	Suspension	Weekly	Immediately dispensed at ambient temperature

Any residual volumes from each dosing occasion will be discarded unless otherwise requested by the Study Director.

Stability of dose formulations: Stability analyses performed previously in conjunction with Test Site Study No. (b) (4) demonstrated that the test item formulation is stable when prepared and stored under the same conditions as those used in the present study, as follows:

- In a concentration range of 10-250 mg/mL for 8 days at room temperature and for at least 3 weeks at -20°C. During the stability analysis, only the stability of the active ingredient (L-tryptophan in 61.34%) was examined. Therefore, there is no information about the stability of the other components in the test item.

Stability data have been retained in the study records of Test Site Study No. (b) (4)

6.2. Preparation Details

The test item will be formulated in the selected vehicle (purified water) at the appropriate concentrations according to the Test Facility's SOPs and the dose levels selected in the study. The formulations will be stirred with magnetic stirrer from the preparation until completion of each treatment.

6.3. Sample Collection and Analysis

Dose formulation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

Dose Formulation Sample Collection Schedule

Sample Type	Concentrations	Stratum	Sampling From	Number of Samples per Concentration			Sample Volume (mL/g)[b]	Intervals[c]
				Collected	Analyzed	Backup		
Concentration analyses	Groups 1 and 3	Middle	Preparation vessel	5	2	3	1	Day 1
Concentration/ Homogeneity[a] analyses	Groups 2 and 4	Top		5	2	3	1	Day 1
		Middle		5	2	3	1	
		Bottom		5	2	3	1	
Concentration analyses	All groups	Middle		5	2	3	1	Week 13

[a] The averaged result from homogeneity analysis will serve as concentration verification.

[b] Sample size: 1 mL for solutions, 1 g for suspensions.

[c] When appropriate, samples will be collected from the formulation (bulk formulation if formulations are not prepared daily) to be used on the day of TK evaluation.

All samples to be analyzed will be stored at -20°C at the Test Facility before shipment to the Test Site for analysis, see Attachment B.

Appendix 1

The analytical laboratory will be notified of the shipment of samples. Upon receipt at the analytical laboratory, the samples will be stored in a controlled room temperature area or dry ice.

6.3.1. Analytical Method

Analyses described below will be performed using a validated HPLC-UV (High Performance Liquid Chromatography with UV detection) analytical method (Test Site Study No. (b) (4) . During the analysis, the active ingredient (L-tryptophan) will be analysed directly. The concentration of the test formulations will be quantified based on its active ingredient content.

6.3.2. Formulation Analysis

Sample Allocation:	2 for analysis, 3 for backup (may be analyzed at the discretion of the Study Director).
Storage Conditions:	Within Stability Data.
Acceptance Criteria:	Concentration: Mean sample concentration results within or equal to ± 15% of theoretical concentration. Homogeneity: Relative Standard Deviation (RSD) of concentrations of ≤ 10% for each group.

7. TEST SYSTEM

Species/Species Family:	Rat.
Strain/Breed:	Wistar Han IGS.
Substrain:	Crl:WI(Han).
Animal Condition:	Naive.
Animal Procurement Method:	Purchased.
Animal Supplier:	(b) (4) .
Animal Supplier Location:	(b) (6)
Number of Males:	50.
Number of Females:	50.

6 alternate animals (3 males and 3 females) will be purchased. If not used in this study, they will be held at the Test Facility.

Age at the Initiation of Dosing:	Approximately 6 weeks.
Weight at the Initiation of Dosing:	120 g to 330 g (males)/110 g to 260 g (females).

Appendix 1

The actual age and weight of the animals at the initiation of dosing will be listed in the Final Report.

7.1. Animal Identification

Method: Subcutaneously implanted electronic identification chip.

7.2. Environmental Acclimation

Acclimation Period: Animals will be acclimatized to the study housing conditions for at least 7 days before the start of dosing.

7.3. Selection, Assignment, Replacement and Disposition of Animals

Selection/Assignment: Animals will be randomly assigned to groups at receipt. **The randomization should results in comparable mean body weight values among the groups (i.e., ± 20% of the mean). Main animals might be replaced by spare animals and/or invert between groups to meet the acceptance criteria.**

Replacement: Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions.

After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-test item-related health issues, or similar circumstances. The alternate animals may be used as replacements on the study within 7 days.

Disposition: The disposition of all animals will be documented in the study records.

8. HUSBANDRY

8.1. Housing

Housing: Group housed (up to 5 animals of the same sex and same dosing group together).

Caging: Plastic cages containing appropriate bedding.

Cage Identification: Color-coded cage card indicating study, group, animal number(s), and sex.

Animals will be separated during designated procedures/activities or will be separated as required for monitoring and/or health purposes, as deemed appropriate by Study Director and/or Clinical Veterinarian. Cages will be arranged on the racks in group order. Where possible, control group animals will be housed on a separate rack from the test item-treated animals.

For the recovery period (treatment-free period), animals may be housed in a room housing recovery animal of the same species from other study(ies), as per the Test Facility SOP.

8.2. Animal Enrichment

Animals will be socially housed for psychological/environmental enrichment and provide with items such as a small amount (handful) of shredded paper in each cage.

It is considered that there are no known contaminants in the enrichment that could interfere with the outcome of the study.

8.3. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	19°C to 25°C.
Humidity:	≥ 35%.
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures).
Ventilation:	10 or more air changes per hour.

8.4. Food

Diet:	Complete rodent diet (Reference No. A04C-12).
Type:	Pellets (alternate diet may be provided on an individual animal basis as approved by the Study Director).
Frequency/Ration:	*Ad libitum*, except during designated procedures.
Analysis:	Diet is sterilised by irradiation and analyzed by the supplier. Each batch of diet is supplied with a certificate of analysis which is verified and authorized for release by a veterinarian, and kept on file at the Test Facility. It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

8.5. Water

Type:	Municipal tap water, softened and filtered (0.2 µm) mains drinking water.
Frequency/Ration:	Freely available to each animal via an automatic watering system (except during designated procedures). Water bottles can be provided, if required.
Analysis:	Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility. It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

Appendix 1

8.6. Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. In the event that animals show signs of illness or distress, the Responsible Veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director. If the condition of the animal(s) warrants therapeutic intervention or alterations in study procedures, the Sponsor Representative will be contacted, when possible, to discuss appropriate action(s). If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or Attending Veterinarian will attempt to consult with the Sponsor Representative prior to responding to the medical crisis, but the Study Director and/or Veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor Representative will be fully informed of any such events.

9. EXPERIMENTAL DESIGN

Main and Recovery Animals

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume[a] (mL/kg)	Dose Concentration (mg/mL)	Number of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Vehicle control	0	10	0	10	10	5	5
2	Test item	500	10	50	10	10	-	-
3	Test item	1000	10	100	10	10	-	-
4	Test item	2000	10	200	10	10	5	5

- = Not applicable.

[a] Based on the most recent body weight measurement.

9.1. Administration/Application of the Test and Control Materials

Route of Administration:	Oral (gavage).
Treatment Frequency:	Daily.
Treatment Duration:	At least 90 days.
Method:	The first day of dosing will be designated as Day 1. The dose formulations will be stirred at receipt and continuously during dosing. The doses will be given by gavage using a syringe with attached cannula.

10. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below will be performed for all main and recovery study animals.

Appendix 1

General In-Life Assessments - Main and Recovery Study Animals

Parameter	Population(s)	Frequency (Minimum Required)	Comments
Mortality	All main study and recovery animals	At least twice daily[a] (morning and end of the working day) beginning upon arrival through termination/release	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings
Cageside Observations	All main study and recovery animals	Before and at least once after dosing on dosing days. At least once daily on non-dosing days, from at least Week -1[b]	Animals will be observed within their cage unless necessary for identification or confirmation of possible findings
Detailed Clinical Observations	All main study and recovery animals	Weekly; from at least Week -1 and throughout the study	Animals are removed from the cage
Arena Observations	All main study and recovery animals	Once before the first administration of the test item and at least weekly thereafter	Animals will be observed for specific clinical signs in a standard arena
Individual Body Weights	All main study and recovery animals	Weekly from at least Week -1 and throughout the study Animals may be weighed more often if necessary in order to monitor the health status	Last body weight before terminal fasting Not collected from animals found dead
Food Consumption	All main study and recovery animals	Weekly for each cage of animals from Day 1 and throughout the study	Quantitatively measured
Behavioral Functional Observational Battery (FOB)	5 main animals/sex/group Examination of Recovery animals (at the end of the recovery period) if findings at Week 13, (at additional cost)	On a suitable day during Week 13, before dosing	As detailed in the section below
Locomotor Activity Test (motor monitor test)			
Ophthalmology	All main and recovery study animals (including alternate animals pretest) Examination of Recovery animals (at the end of the recovery period) if findings at Week 13, at additional cost)	Once pretest (all animals) At the end of the dosing period (Week 13 - Groups 1 and 4 main study animals only)	See details in the section below
Estrous Cycle	All main study and recovery females	On the day of scheduled necropsy	Vaginal smears will be taken to determine the stage of estrus for each female

[a] Except on days of receipt and necropsy where frequency will be at least once daily.

[b] For observations that cannot be attributed to an individual animal due to social housing, the observation will be noted to each animal in the socialized group.

Appendix 1

10.1. Behavioral Functional Observational Battery (FOB)

Behavorial tests will be conducted in group-housed animals.

FOB parameters will be evaluated per Test Facility SOPs and study-specific procedures (if any) as follows:

FOB Measurements

Functional Domains/ Parameters	Assessment Occasion			Type of Data	Rating Scale or Unit of Measurement
	Home Cage	During Handling	Open Field		
Activity Domain					
Arousal/Alertness	-	-	X	Categorical	-2 to 2
Posture/Body carriage	X	-	-	Categorical	-2 to 0
Stereotypy	X	-	X	Categorical	0 to 4
Rearing	-	-	X	Counts	Counts
Appearance	-	-	X	Categorical	0 to 2
Excitability Domain					
Vocalizations	-	-	X	Categorical	0 to 1
Startle response	-	-	X	Categorical	-1 to 1
Ease of removal	-	X	-	Categorical	-1 to 2
Handling reactivity	-	X	-	Categorical	-1 to 2
Convulsions	X	-	X	Categorical	0 to 4
Autonomic Domain					
Exophthalmos	-	-	X	Categorical	0 to 1
Lacrimation	-	-	X	Categorical	0 to 2
Erected fur (piloerection)	-	-	X	Categorical	0 to 1
Pupil response	-	-	X	Categorical	0 to 2
Salivation	-	-	X	Categorical	0 to 2
Defecation	-	-	X	Categorical	-1 to 1
Palpebral closure/Ptosis	X	-	X	Categorical	0 to 2
Neuromuscular Domain					
Gait/Mobility	-	-	X	Categorical	0 to 3
Grip strength (forelimbs)	-	-	X	Continuous	Grams
Grip strength (hindlimbs)	-	-	X	Continuous	Grams
Air righting reflex	-	-	X	Categorical	0 to 2
Tremor	X	-	X	Categorical	0 to 3
Body tone	-	-	X	Categorical	-1 to 1
Sensorimotor Domain					
Touch response/Tactile reflex	-	-	X	Categorical	-1 to 1
Tail pinch response	-	-	X	Categorical	-1 to 1
Physiological Domain					
Respiration	-	-	X	Categorical	-1 to 2
Body temperature	-	-	X	Continuous	Degree Celsius

A detailed description of the measurements/scoring performed during the FOB will be presented in the Study Report. Any other clinical and/or behavioral abnormalities will also be noted and presented in the Study Report.

Appendix 1

In a first step, the animal will undergo neurobehavioral evaluation in the home cage with ranking of posture, palpebral closure, stereotypies, convulsions, and tremors.

In a second step, the ease of removal of the animal from the home cage and its reactivity to handling during removal and transfer to the open field will be scored.

In a third step, the animal will be placed in a 50 x 50 x 20 cm black open field and observed for 2 minutes in freely moving conditions. Arousal, vocalizations, respiration, gait, stereotypies, convulsions and tremors will be ranked. The number of rearing occasions will be counted.

At the end of the 2-minute observation period, defecation (aspect of feces) will be ranked and the animals will undergo a series of additional observations and tests (from the least to the most invasive).

- The observer will handle the animals and rank fur appearance, lacrimation, salivation, exophthalmos, palpebral closure, and erected fur (piloerection).
- The animal will be tested for various reflexes such as response to a touch of the body with a rod, startle response (using a clicker), tail pinch response and pupil response.
- Body temperature will be measured using a rectal probe.
- The animal will be ranked for body tone, forelimbs and hindlimbs grip strength and air righting reflex (from a height of 30 cm). Forelimbs and hindlimbs grip strength will be measured with a T-shaped bar connected to a dynamometer that determines the maximal force developed by the limbs when the operator pulls the animal away from the bar. The measure will be performed 3 times (individual values of repeated measurements kept in the raw data but not reported) and the mean value will be calculated and reported.

10.2. Locomotor activity test

A locomotor activity test will be performed in an open field in order to assess reactivity to a novel environment and motor activity. Activity will be monitored by a photobeam analysis system (Motor Monitor supplied by (b) (4)) for 1 hour. The arena is divided by 7 and 15 equally spaced infrared beams in width and length, respectively; the time and the number of beams interrupted by the animal will be recorded. Motor activity is divided into 2 types of activity: Ambulatory activity (large animal movements like walking) and fine movements (including grooming and head movements). The proportion of beams blocked by the rat in each type of activity will be calculated.

10.3. Ophthalmic examinations

Animals: Additional examination of Groups 2 and 3 at the end of the dosing period and/or of recovery animals at the end of the recovery period will be conducted only if considered necessary to further investigate initial findings (to be confirmed by Study Plan amendment- at additional cost).

Procedure: A mydriatic agent (Tropicamide) will be instilled into the eyes before examination. Examination of adnexa, optic media and fundus will be performed by indirect ophthalmoscopy. An examination using a slit lamp may be performed if necessary to examine the anterior segment of the eye (including the lens).

Evaluation: The interpretation of results will be done by a Veterinary Ophthalmologist.

Appendix 1

11. CLINICAL PATHOLOGY

11.1. Sample Collection

Clinical Pathology Sample Collection

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	Hormone Analysis	Urinalysis
1 to 4 (main animals only)	Day 91 or Day 92	X	X	X	X[c]	X
1 and 4 (recovery animals only)	Day 120	X	X	X	X[c]	X
Unscheduled euthanasia[a] (when possible)	-	X	X	X	-	-
Fasting (overnight, about 16hr):		-	-	Yes	Yes	Yes
Method/Comments:		Submental vein sinus or sublingual vein under slight anesthesia (or other site as deemed necessary)				Deprived of food and water ad libitum
Target Volume (mL)[b]:		0.5	0.9	1.0	1.3	As available
Anticoagulant:		EDTA-K_2	Trisodium citrate	None	None	-
Special Requirements:		-	-	-	**Samples to be kept at room temperature for at least 30 minutes to allow clotting (maximum up to 2 hours)**	-
Processing:		None	Plasma	Serum	Serum	-

X = Sample to be collected; - = Not applicable; hr = Hour.

[a] Order of priority to be defined if appropriate.

[b] Additional samples may be obtained (e.g., due to clotting of non-serum samples) if permissible sampling frequency and volume are not exceeded.

[c] **Between 7.00 and 10.30 a.m. because of diurnal variation of hormone levels.**

Appendix 1

11.2. Hematology

Hematology Parameters

Red blood cell count	Platelet count
Hemoglobin concentration	Mean Platelet volume
Hematocrit	White blood cell count
Mean corpuscular volume	Neutrophil count
Red Blood Cell Distribution Width (gated)	Lymphocyte count
Mean corpuscular hemoglobin concentration	Monocyte count
Mean corpuscular hemoglobin	Eosinophil count
Mean Platelet Thrombocyte Volume	Basophil count
Reticulocyte count	Large unstained cells count

A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. Individual blood smears may be examined to confirm certain analyzer results, as required by SOP.

If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a Study Plan amendment.

Morphology findings that require confirmation, as required by SOP, will be reviewed by a clinical pathologist or designee at (b) (4).

11.3. Coagulation

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time

11.4. Clinical Chemistry

Clinical Chemistry Parameters

Alanine aminotransferase	Albumin
Aspartate aminotransferase	Globulin (calculated)
Alkaline phosphatase	Albumin/Globulin ratio
Total bilirubin[a]	Glucose
Urea nitrogen/Urea	Cholesterol
Creatinine	**High Density Lipoprotein**
Calcium	**Low Density Lipoprotein**
Phosphorus	Triglycerides
Bile acids	Sodium
Total protein	Potassium
Gamma glutamyl transferase	Chloride

[a] When total bilirubin is > 10 µmol/L, direct bilirubin will also be measured and indirect bilirubin will be calculated.

Appendix 1

11.5. Urinalysis

Urinalysis Parameters

Volume[a] Color Appearance/Clarity Specific gravity pH **Nitrite**	Protein Glucose Bilirubin Ketones Blood **Osmolality** **Sediment**

[a] Except when collected at necropsy or by puncture.

11.6. Bone Marrow Smear Evaluation

Bone marrow smears will be collected as described in the terminal procedures table (see Attachment A) and will be staining using the Aerospray automaton (May-Grünwald Giemsa method).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the Pathologist and the Sponsor.

11.7. Thyroid Hormone Analysis

11.7.1. Sample preparation

Sample preparation:

Centrifugation	**Volume Serum Aliquot 1**	**Volume Serum Aliquot 2**	**Volume Serum Aliquot 3**	**Volume Serum Aliquot 4**	**Freezing**	**Specific Request**
1800 g 10 minutes Approximately +21°C	At least 150 µL	At least 150 µL	At least 100 µL	At least 100 µL	-70°C/-90°C	Samples to be kept at room temperature for at least 30 minutes to allow clotting (maximum up to 2 hours)

Theoretical number of serum samples: 100 samples x 4 aliquots.

The samples will be dispatched in dry ice with recording device to Test Site after the last sampling occasion (see Attachment B).

After reception at Test Site, the samples will be immediately analyzed or stored at (-80 ± 10 °C) until analysis.

11.7.2. Thyroid hormone analysis

Samples from all animals will be assessed for T3, T4 and TSH levels (Study Phase No. (b) (4)).

Levels of thyroid hormones will be determined using validated methods in compliance with relevant SOPs. Details will be given in the phase report.

Appendix 1

Each assay will consist of:

- blank samples (will be documented in the raw data and reported in a phase report)
- calibration curve, calculated by at least five calibration levels
- QC samples (assayed in duplicate in case of TSH and in triplicate in case of T3 and T4 hormones, concentrations will be documented in the raw data and reported)
- study samples

Stability in rat serum: 132 days for T3 and T4, and 142 days for TSH when stored at a temperature set to maintain -80 ± 10 ºC.

11.7.3. Acceptance criteria

Back-calculated results of each calibration point should be within ± 25% of their nominal values, except of 0 level.

Results of QC samples should be within ± 25% of their nominal values and valid results should be accepted at least two out of three results for each QC level in case T3 and T4 measurements and at least one out of two results for each QC level in case of TSH.

Invalid runs will be automatically repeated. If re-assay of samples will be needed, the reason will be documented in the raw data and reported.

In the case of concentration values above the highest validated level, samples will be diluted with the zero calibrator (will be documented and reported) to obtain a concentration within the validated range. If any dilution will be prepared, then it will be documented in the raw data and reported in the study report.

Any sample not required for analysis will be discarded following acceptance of the results of the hormone analysis by the Contributing Scientist #1 and Study Director after the finalization of the study report.

12. TERMINAL PROCEDURES

Terminal procedures are summarized in the following tables:

Main Study Animals

Group No.	Scheduled Euthanasia Day	Necropsy Procedures			Histology Processing	Microscopic Evaluation
		Necropsy	Tissue Collection	Organ Weights		
Found dead or unscheduled euthanasia	-	X	Full list[a]	-	Full list[a]	Full list[a]
1 and 4	91-92	X	Full list[a]	Full list[a]	Full list[a]	Full list[a]
2 and 3	91-92	X	Full list[a]	Full list[a]	Gross lesions Target tissues[b]	Gross lesions Target tissues[b]

X = Procedure to be conducted; - = Not applicable.

"Histology Processing": Embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

[a] See Attachment A for list of tissues applicable to each procedure.

[b] Any target tissues identified by the Study Pathologist during microscopic evaluation of full list animals will be communicated to the Study Director, then processed, evaluated and reported in non-full list animals.

Appendix 1

Recovery Animals

Group No.	Scheduled Euthanasia Day	Necropsy Procedures			Histology Processing	Microscopic Evaluation
		Necropsy	Tissue Collection	Organ Weights		
Found dead or unscheduled euthanasia	-	X	Full list[a]	-	Full list[a]	Full list[a]
1 and 4	120	X	Full list[a]	Full list[a]	Gross lesions Target tissues[b]	Gross lesions Target tissues[b]

X = Procedure to be conducted; - = Not applicable.

"Histology Processing": Embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

[a] See Attachment A for list of tissues applicable to each procedure.

[b] Any target tissues identified by the Study Pathologist during microscopic evaluation of full list animals will be communicated to the Study Director, then processed, evaluated and reported in non-full list animals.

12.1. Method of Euthanasia

Animals will be euthanized by carbon dioxide inhalation followed by exsanguination or by isoflurane inhalation followed by exsanguination for unscheduled necropsy/blood sampling.

12.2. Unscheduled Euthanasia

Main study and recovery animals to be euthanized for humane reasons before the scheduled time will undergo a final clinical observation, and biological samples will be obtained if possible as specified in relevant sections.

12.3. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia will be fasted overnight before necropsy and will have a terminal body weight recorded. When applicable, the animals will be euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, will be necropsied throughout the day.

12.4. Necropsy

Animals as detailed in the terminal procedures table will be subjected to a complete necropsy examination, which will include evaluation of the carcass and musculoskeletal system, all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Images may be generated for illustration of or consultation on gross observations, at the discretion of the Study Pathologist and/or the Study Director. These images will not be used for data generation or interpretation and will not be archived or included in the Final Report.

Any remaining tissues not required for histopathology or retention may be harvested from the carcass of vehicle control animals before disposal. These tissues, if collected, may be used for validation or investigational purposes and as such are not part of this study and will not interfere with the study objectives.

12.5. Organ Weights

The organs detailed in the tissue table in Attachment A will be weighed at necropsy. Paired organs will be weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as an observation comment. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight will be calculated.

12.6. Tissue Collection and Preservation

Representative samples of tissues will be collected and preserved in 10% neutral buffered formalin, as detailed in the tissue table in Attachment A. Additional tissue samples may be collected to elucidate abnormal findings.

13. HISTOLOGY AND MICROSCOPIC EVALUATION

13.1. Histology

Tissues as detailed in the tissue table in Attachment A will be processed at the Test Facility.

The same sampling and trimming procedures will be used for all applicable tissues in all applicable dose groups.

For the testicles of males from Groups 1 and 4 main animals, detailed qualitative examination will be made taking into account the tubular stages of the spermatogenic cycle. In addition to the haematoxylin and eosin-stained slide, an additional slide will be prepared and examined, stained with PAS. The examination will be conducted in order to identify treatment related effects such as missing germ cell layers or types, retained spermatids, multinucleate or apoptotic germ cells and sloughing of spermatogenic cells into the lumen. Any cell- or stage-specificity of testicular findings will be noted.
Vaginal smears performed before necropsy will be stained with hematoxylin and eosin after air-drying and ethanol fixation at the Test Facility.

Sperm analysis will be performed for Groups 1 and 4, using automated equipment (b) (4)). The left cauda epididymis will be sampled and used for the assessment of caudal sperm reserves and sperm motility, including progressive motility. Sperm counts will be performed using the left testis following removal of the tunica albuginea. In the case of an abnormality of the left epididymis or testis, the right organs may be used for sperm analysis.

Sperm morphology will be evaluated for Groups 1 and 4, (at least 200 sperm per sample, where possible). The numbers of sperm with each type of abnormality will be recorded. Slides for assessment of sperm morphology will be prepared for all surviving males from all groups. Evaluation will be performed for the control and high dose groups in first instance. If a treatment-related effect is found, the intermediate dose groups will also be examined.

13.2. Microscopic Evaluation

Histopathological evaluation will be performed by a veterinary pathologist with training and experience in laboratory animal pathology.

Histopathological examination will be performed for all gross lesions from animals in all groups, except those for which the diagnosis is judged unnecessary for the outcome of the study by the Pathologist.

Special stains may be used at the discretion of the Pathologist to further characterize lesions and changes identified during routine evaluation of individual animals. Any special stains will be documented in the individual animal data. Any additional stains or evaluations, if deemed necessary by the Pathologist, may be added by Study Plan amendment following discussion with the Study Director and in consultation the Sponsor.

Efforts will be made to evaluate all Study Plan-required tissues microscopically; however, it is not always feasible for every Study Plan-required tissue to be present on every slide. Study Plan-required tissues that are not examined will be documented in the histopathology data and the impact of these missing tissues on the study will be documented in the Pathology Report.

Images may be generated for illustration of or consultation on histological observations. These images will not be used for data generation or interpretation and will not be archived or included in the Final Report.

13.3. Pathology Peer Review

A Pathology Peer Review will be conducted according to internal procedures by another Pathologist at the Test Facility. The Peer Review Statement or equivalent documentation will be included as an appendix to the Final Report or in the study file.

Any additional Peer Reviews of the histological sections will be documented in an amendment to this Study Plan (these may be at additional cost and may impact reporting dates).

14. STATISTICAL ANALYSIS

Any data collected during the predose period will be tabulated, summarized, or statistically analyzed. All statistical analyses will be performed within the respective study phase, unless otherwise noted. Numerical data collected on scheduled occasions will be summarized and statistically analyzed as indicated below according to sex and occasion.

14.1. Constructed Variables

Body Weight Changes:	Calculated between each scheduled interval.
Food Consumption:	Calculated between each scheduled interval (individual data only) and as specified above for bodyweight gains. Summarization and statistical analysis intervals will reflect the same intervals as the bodyweight gains. In case of any animal replacement, the statistical analysis of food consumption data cannot be performed due to data acquisition system constraints.
Organ Weight Relative to Body Weight:	Calculated against the terminal body weight for scheduled intervals.

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Organ Weight Relative to Brain Weight: Calculated against the brain weight for scheduled intervals.

Additional or alternative body weight or food consumption intervals may be evaluated to elucidate study results at the discretion of the Study Director.

14.2. Descriptive Statistical Analyses

Means, standard deviations (or % coefficient of variation or standard error, when deemed appropriate), ratio, percentages, numbers, and/or incidences will be reported as appropriate by dataset.

14.3. Inferential Statistical Methods

All statistical tests will be conducted at the 5% significance level. All pairwise comparisons will be conducted using two-sided tests and will be reported at the 1% and 5% levels, unless otherwise noted.

The pairwise comparisons of interest are listed below:

Group 2	vs.	Group 1
Group 3	vs.	Group 1
Group 4	vs.	Group 1

Analyses will be performed according to the matrix below when possible, but will exclude any group with less than 3 observations.

Statistical Matrix

Variables for Inferential Analysis	Statistical Method		
	Parametric/ Non-Parametric	Non-Parametric	Incidence
Body weight	X	-	-
Body weight gains	X	-	-
Food consumption	X	-	-
Hematology variables	X	-	-
Coagulation variables	X	-	-
Clinical chemistry variables	X	-	-
Urinalysis variables	X	-	-
Thyroid hormones[a]	X	-	-
FOB qualitative variables	-	-	-
FOB quantitative variables	X	-	-
Organ weights	X	-	-
Organ weight relative to body weight	X	-	-
Organ weight relative to brain weight	X	-	-
Sperm morphology	-	X	-
Sperm count and motility	X	-	-

X = Statistical analysis performed.

- = Statistical analysis not performed.

[a] Analysis to be performed at the Test Site.

14.4. Parametric/Non-Parametric

Levene's test will be used to assess the homogeneity of group variances.

The groups will be compared using an overall one-way ANOVA F-test if Levene's test is not significant or the Kruskal-Wallis test if it is significant. If the overall F-test or Kruskal-Wallis test is found to be significant, then pairwise comparisons will be conducted using Dunnett's or Dunn's test, respectively.

14.5. Non-Parametric

The groups will be compared using an overall Kruskal-Wallis test. If the overall Kruskal-Wallis test is found to be significant, then the above pairwise comparisons will be conducted using Dunn's test.

14.6. For Data Generated Outside (b) (4)

Sperm count, (b) (4) and motility data will be analysed using a (b) (4) software package. Levene's test will be used to test the equality of variance across groups and Shapiro-Wilk's test will be used to assess the normality of the data distribution in each group. Data with homogeneous variances and normal distribution in all groups will be analysed using ANOVA followed by Dunnett's test. Data showing non-homogeneous variances or a non-normal distribution in at least 1 group will be analysed using Kruskal-Wallis test followed by the Wilcoxon's rank sum test.

15. COMPUTERIZED SYSTEMS

The following computerized systems may be used in the study. The actual computerized systems will be documented in the Final Report.

Computerized Systems

System Name	Description of Data Collected and/or Analyzed
(b) (4)	Environmental Monitoring System
	Test item receipt, accountability and/or formulation activities; in-life; clinical pathology; postmortem; statistical analysis
(b) (4)	Safety Assessment document management and publishing Collection of 21 CFR Part 11 compliant signature
DocuSign™	Electronic Signature
(b) (4)	Deviation information library
	Statistical Analysis
	Locomotor activity test
	Sperm Analyser
	Hematology Parameters (interfaced to (b) (4)
	Coagulation Parameters (interfaced to
	Coagulation Parameters (interfaced to
	Biochemistry Parameters (interfaced to
	Urine Parameters (interfaced to (b) (4))
	Sample tracking
	System control, data acquisition and integration

Microsoft® Excel (version 2003 or higher) may be employed to present certain results and perform associated calculations.

Appendix 1

Data for parameters not required by the Study Plan, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by the Study Plan and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

16. REGULATORY COMPLIANCE

The study will be performed in accordance with OECD Principles of Good Laboratory Practice as required in Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004, Bonnes Pratiques de Laboratoire, Ministère de l'Emploi et de la Solidarité Française, No. 2000/5bis, arrêté du 14/03/2000, Good Laboratory Practices in Article Annexe II de l'article D523-8 du code de l'environnement du 16 octobre 2007.

If applicable, the regulatory compliance to applicable regulations of electronic signature system developed and used by the Sponsor is under his responsibility.

OECD Principles of Good Laboratory Practice are accepted by Regulatory Authorities throughout the European Union, United States of America (FDA and EPA) and Japan (MHLW, MAFF and METI) and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

In order to enable the results of the study phases conducted in Hungary to meet the requirements for regulatory submission and/or safety assessment, the study will be performed in compliance with the principles of Good Laboratory Practice Regulations as requested by the Sponsor and specified in the Hungarian Good Laboratory Practice Regulations of 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities. Those regulations correspond to the OECD Principles of Good Laboratory Practice (OECD GLP, ENV/MC/CHEM (98) 17) and as accepted by Regulatory Authorities throughout the European Union, United States of America, Japan, and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

17. QUALITY ASSURANCE

17.1. Test Facility

The Test Facility Quality Assurance Unit (QAU) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAU will review the Study Plan (and any amendments), conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to assure that it accurately describes the methods and Standard Operating Procedures and that the reported results accurately reflect the raw data of the study.

All Quality Assurance documents will be retained by the Test Facility as their property and will not be returned to the Study Sponsor.

17.2. Test Site(s)

For all study phases inspected by Test Site QAU(s), copies of each inspection report will be made available to the Study Director, Test Facility Management, and the Test Facility Lead QA.

18. AMENDMENT(S) AND DEVIATIONS

Changes to the approved Study Plan shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary Study Plan changes in advance with the Sponsor.

All Study Plan and SOP deviations will be documented in the study records. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

Deviations from the Study Plan and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the Principal Investigator, and reported to the Study Director for authorization/acknowledgement.

19. RETENTION AND DISPOSITION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, Study Plan, retained samples and specimens, and the Final Report will be archived at the Final Report issue. All materials generated by (b) (4) from this study will be transferred to a (b) (4) archive and kept for a period of 15 years following the date of issue of the Final Report.

Disposition of residual/retained analytical samples will be as described in the table below.

Disposition of Residual/Retained Samples

Sample Type	Disposition	Schedule
Analytical (and test item used in analysis)	Discard residual volumes	Samples will be maintained for the defined period of stability, and then discarded
Thyroid hormones	Discard residual volumes	Samples will be maintained for a maximum of 6 months following issuance of the first full Draft Report after which samples will be managed as defined in the 'disposition' column as requested and authorized by the Study Director and in consultation with the Sponsor

Records to be maintained will include, but will not be limited to, documentation and data for the following:

- Deviations, Study Plan amendments and Study Plan.
- Study schedule.
- Study-related correspondence.
- Test system receipt, health, and husbandry.
- Test materials receipt, identification and preparation.
- Reserve sample.
- In-life measurements and observations.
- Clinical pathology sample collection and evaluation.
- Hormone samples collection and analysis.
- Gross and microscopic observations and related data.
- Organ weight measurements.
- Statistical analysis results.
- Original signed Final Report.

Appendix 1

Original Study Plan and amendment(s) signed by the Sponsor (wet signature or e-signed documents) will be maintained either at (b) (4) or archived at the Sponsor under his responsibility and should be made available in case of monitoring authority request.

The disposition of the original documents signed by the Sponsor will be described in the Study Report.

20. STUDY CLASSIFICATION

Submission Study Category:	Toxicology.
Submission Study Type:	Repeat dose toxicity.
Study Design:	Parallel.
Primary Treatment CAS Registry No.:	73-22-3.

21. REPORTING

The Study Sponsor will be informed promptly of any significant findings at any time during the study.

A Draft Report with extended methods will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft and Final Report(s), provided in Adobe Acrobat PDF format (hyperlinked and searchable at final), along with a Microsoft Word version of the text. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Test Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation.

22. JUSTIFICATION AND GUIDELINES

22.1. Justification of Test System and Number of Animals

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models which do not use live animals currently do not exist.

The rat was chosen as the animal model for this study as it is an accepted rodent species for toxicity testing by regulatory agencies.

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the test item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

22.2. Justification of Route and Dose Levels

The oral route of administration was selected because this is the route of administration specified in the OECD 408 and OCSPP guidelines. The dose levels were set by the Study Director in agreement with the Study Monitor based on the available information of the chemical nature, characteristics of the test item, and available data and information from previous experimental work, including the results of a Dose Range Finding (DRF) study (Study code 21/300-101PE). Based on those results where the test item was given at 500, 1000 and 2000 mg/kg bw in distilled water, 2000 mg/kg bw/day was selected as the High dose for this study. The low and intermediate dose levels of 500 and 1000 mg/kg/day were selected to derive a dose-response for any effects that may be observed.

22.3. Guidelines for Study Design

The design of this study was based on the study objective(s), the overall product development strategy for the test item, and the following study design guidelines:

- OECD Guideline 408 (2018). Repeated Dose 90-day Oral Toxicity Study in Rodents.
- EPA Health Effects Test Guideline OPPTS 870.3100: 90-Day Oral Toxicity in Rodents.

23. ANIMAL WELFARE

The study design was reviewed and approved by the ethical committee of the Test Facility as per the Standard Project Authorization No. (b) (4).

The study design, animal housing and associated procedures are in general compliance with the following animal health and welfare guidelines:

- Guide for the care and use of laboratory animals, 2011.
- Decree No. 2013-118 relating to the protection of animals used in scientific experiments described in the Journal Officiel de la République Française on 01 February 2013.
- Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

The Test Facility is AAALAC accredited.

By approving this Study Plan, the Sponsor affirms that there were no other alternative experimental methods other than the use of live animals to achieve the required objectives, that the harm-benefit analysis of the project was performed and that this study does not unnecessarily duplicate any previous experiments.

Appendix 1

ATTACHMENT A

Tissue Weighing, Collection, Processing and Evaluation Table

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Animal ID	-	X	-	-
Artery, aorta	-	X	X	X
Body cavity, nasal	-	X	-	-
Bone marrow, sternum	-	X	X	X
Bone marrow smear	-	X[a]	-	-
Bone, femur	-	X (1)	X (1)	X (1)
Bone, sternum	-	X	X	X
Brain	X	X	X	X
Epididymis[e]	X (2)	X (2)[b]	X (2)	X (2)
Esophagus	-	X	X	X
Eye	-	X (2)[b]	X (2)	X (2)
Ganglion, dorsal root, lumbar	-	X	-	-
Gland, adrenal	X (2)	X (2)	X (2)	X (2)
Gland, clitoral	-	X (2)	-	-
Gland, lacrimal	-	X (2) (extra-orbital)	-	-
Gland, Harderian	-	X (2)	X (1)	X (1)
Gland, mammary	-	X	X	X
Gland, parathyroid	-[d]	X (2)	X (2)	X (2)
Gland, pituitary	X	X	X	X
Gland, preputial	-	X (2)	-	-
Gland, prostate	X	X	X	X
Gland, salivary, submandibular	-	X (2)	X (1)	X (1)
Gland, salivary, sublingual	-	X (2)	-	-
Gland salivary, parotid	-	X (2)	-	-
Gland, seminal vesicle **with coagulating gland**	X (2)	X (2)	X (2)	X (2)
Gland, thyroid	X (2)	X (2)	X (2)	X (2)
Gland, Zymbal's	-	X (2)	-	-
Gut-associated lymphoid tissue[c]	-	X	X	X
Heart	X	X	X	X
Joint, femorotibial	-	X (1)	X (1)	X (1)
Kidney	X (2)	X (2)	X (2)	X (2)
Large intestine, cecum	-	X	X	X
Large intestine, colon	-	X	X	X
Large intestine, rectum	-	X	X	X
Larynx	-	X	-	-
Liver	X	X	X	X
Lung	-	X	X	X
Lymph node, mandibular	-	X (2)	X (1)	X (1)
Lymph node, mesenteric	-	X	X	X
Macroscopic abnormalities	-	X	X	X
Muscle, skeletal	-	X (2)	X (1)	X (1)
Nerve, optic	-	X (2)[b]	X (2)	X (2)
Nerve, sciatic	-	X (2)	X (1)	X (1)
Nerve, tibial	-	X (2)	-	-

Appendix 1

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Ovary	X (2)	X (2)	X (2)	X (2)
Olfactory bulbs	-	X	X	X
Oviduct	-	X (2)	-	-
Pancreas	-	X	X	X
Skin	-	X	X	X
Small intestine, duodenum	-	X	X	X
Small intestine, ileum	-	X	X	X
Small intestine, jejunum	-	X	X	X
Spinal cord	-	X	X	X
Spleen	X	X	X	X
Stomach	-	X	X	X
Testis[e]	X (2)	X (2)[b]	X (1)	X (1)
Thymus	X	X	X	X
Tongue	-	X	X	X
Trachea	-	X	X	X
Ureter	-	X (2)	-	-
Urinary bladder	-	X	X	X
Uterus/Cervix	X	X	X	X
Vagina	-	X	X	X
Vaginal smear	-	X	X	-

X = Procedure to be conducted; - = Not applicable; (1) = One side; (2) = Both sides.

Macroscopic abnormalities in the organs listed and in other organs will be sampled at necropsy, processed for histology and examined microscopically.

[a] 2 bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry.

[b] Eyes and optic nerves are preserved in Davidson's fixative. Testes and epididymides are preserved in modified Davidson's fixative.

[c] From small intestine: Peyer's patch or solitary lymphoid follicle.

[d] Weigh with gland, thyroid.

[e] For terminal and recovery males from groups 1 and 4 (except any premature decedent), the left testis and epididymide will be dedicated for sperm analysis, the right organs for the histopathological examination. Both testes and epididymides will be weighed (separately) as well as the left cauda of the epididymide dedicated for sperm analysis. After analysis of sperm, the remainder of the left epididymide could be preserved.

Appendix 1

ATTACHMENT B

Shipment of Samples and Study Records

Matrix	Purpose	Day/ Week/ Aliquot	Proposed Shipment Date	Conditions for Shipment	Recipient/Address
Formulations	Dose Formulation Analysis	Day 1 (2 first aliquots)	19 Oct 2022	Dry Ice	(b) (4), (b)(6)
		Week 13 (2 first aliquots)	17 Jan 2023	Dry Ice	
Serum	Thyroid Hormone Analysis	All	15 Feb 2023	Dry ice	

Appendix 1

SPONSOR APPROVAL

The signature of the Sponsor Representative below indicates approval of this Study Plan.

DocuSigned by:
(b)(6)

Sponsor Representative

Appendix 1

TEST FACILITY APPROVAL

All electronic signatures appear at the end of the document upon finalization.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 1

SIGNATURE(S) FOR DOCUMENT: (b) (4) - Study Plan

TFM Approval-GLP:	I approve the Study Director identified in this document and management's responsibility to the study as defined by the relevant GLP.
Name:	(b)(6)
Electronically Signed in (b) (4)	04-Oct-2022 14:51:07 (UTC+00:00) Timestamp

Study Director Approval:	I approve this document.
Name:	(b)(6)
Electronically Signed in (b) (4)	04-Oct-2022 15:15:50 (UTC+00:00) Timestamp

Appendix 2

CJ Research Institute of Biotechnology

55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, 16495, Korea, CJ BLOSSOM PARK

www.cj.co.kr

TEL: 031) 8099-2450 FAX: 031) 8099-2918

Certificate of analysis

Certificate No.	2021-PR-213	Receipt No.	2021-AN-178
Client		Date of Receipt	2021-10-27
Client Name		Date of Test	2021-10-28
Client Tel		Use of Report	Reference test
Client Address			
Test Sample	L-tryptophan (TRP Pro)		
Manuf. Date	2021.10.05		
Lot. No	(b) (4)		
Quantity (kg)			

Test Item(s)	Test Result	Test method used
L-Tryptophan (dry basis)	(b) (4)	HPLC
Loss on drying		AOAC 934.01

* Information

* Temperature: (15~25)℃, Relative Humidity: (10~80)%
* The results shown in this test report refer only to the sample tested unless otherwise stated.
* The Test Report cannot be reproduced, except in full.

(b)(6)

November 3, 2021

CJ Research Institute of Biotechnology

CJ BIO-AD form 100-01 REV.01

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 3

(b) (4)

FINAL ANALYTICAL PHASE REPORT

Dose Formulation Analysis

Test Facility Study No. (b) (4)

Sponsor Reference No. (b) (4)

Test Site Study Code: 21/300-420AN

90-Day Repeated Dose Toxicity Study of TRP Pro by the Oral (gavage) Route in the Wistar Han IGS Rat with a 4-week Recovery Period

GLP Study

Principal Investigator: (b) (6)

SPONSOR:
CJ CheilJedang Corporation
55-42 Beongil Gwanggyo-ro, Yeongtong-gu
Suwon-si
16495 Gyeonggi-do
Republic of Korea

(b) (4)

Appendix 3

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Appendix 3

STATEMENT OF THE PRINCIPAL INVESTIGATOR

This phase has been performed in accordance with the Study Plan, the Study Report of Validation of the Analytical Method and the Principles of Good Laboratory Practice (Hungarian GLP Regulations of 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.).

I the undersigned declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study. By virtue of my dated signature, I accept the responsibility for the validity of the data.

(b)(6)

10 July 2021
Date

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 3

STATEMENT OF THE TEST SITE MANAGEMENT

According to the conditions of research and development assignment between (b) (4) (as Test Facility) and (b) (4) as Test Site), the phase titled "Dose Formulation Analysis" has been performed in compliance with the Study Plan and the Principles of Good Laboratory Practice.

(b)(6)

10 July 2023
Date

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 3

TEST SITE QUALITY ASSURRANCE STATEMENT

Test Site Phase Code: 21/300-420AN
Testing Facility Study No. (b) (4)
Phase Title: Dose Formulation Analysis
Test Item: TRP Pro

This Phase has been audited by (b) (4) in accordance with the applicable Good Laboratory Practice regulations.

All inspections, data reviews and the report audit were reported in written form to the Principal Investigator and Test Site Management; and the copies of the report were available to the Study Director, Test Facility Management and Test Facility QAU. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to		
		Test Site Management	Principal Investigator	Test Facility
21 October 2022	Study Plan Amendment 01	21 October 2022	21 October 2022	21 October 2022
28 March 2023	Study Plan Amendment 04	28 March 2023	28 March 2023	28 March 2023
22 November 2022	Formulation / Solution Preparation	22 November 2022	22 November 2022	N/A
22 November 2022	Sampling	22 November 2022	22 November 2022	N/A
23 November 2022	Measurement / Observation	23 November 2022	23 November 2022	N/A
30 March 2023	Draft Phase Report and Raw Data	30 March 2023	30 March 2023	30 March 2023
10 July 2023	Final Phase Report	10 July 2023	10 July 2023	10 July 2023

N/A: these audits were not reported to the Test Facility because they were process based inspections

In addition to the above-mentioned audits, (which may include study specific inspections and/or relevant process based inspections) routine facility inspections were also conducted.

The Final Phase Report reflects the raw data and accurately and completely describes the methods and procedures of the study.

(b)(6)

10 July 2023
Date

Appendix 3

1. OBJECTIVE

The concentration of L-tryptophan (TRP Pro) in the prepared formulation samples were determined on two analytical occasions during the GLP 90-Day Toxicity Study in Rats (Test Facility Study No. (b) (4)

On the first occasion (Day 1), the control and test item formulations were prepared on 17 October 2022 and sampled on 18 October 2022 (except the control formulations, what were prepared and sampled on 13 October 2022). The samples were shipped to the analytical laboratory of the Test Site on 24 October 2022 and received on 25 October 2022 in good conditions. The samples were measured on 26 October 2022. The samples were stored in freezer (-20°C) until analysis.

On the second occasion (Day 84), the control formulation was prepared and sampled on 06 January 2023, the test item formulations were prepared and sampled on 09 January 2023.

In order to confirm the stability of the test item formulations applying continuous stirring for 8 days, the above prepared test item formulations were re-sampled on 17 January 2023.

The samples were shipped to the Test Site on 17 January 2023 and received on 18 January 2023 in good conditions. The samples were stored in freezer (-20°C) until analysis.

The homogeneity and concentrations of the test item samples were analysed by the previously validated HPLC-UV method (Test Site Study Code: 21/300-316AN). The measurement is based on the evaluation of selected chromatographic peak as marker for the test item according to the retention time of the reference item (L-tryptophan). The test item is an UVCB substance mixture (according to its purity), therefore only the main detectable (L-tryptophan as active ingredient) peak is used. The method used was considered to be appropriate for purpose.

2. SCHEDULE

Start of the formulation analysis: 26 October 2022

End of the formulation analysis: 20 January 2023

Draft Phase Report (QAd): 31 March 2023

Final Phase Report: 10 July 2023

3. SPONSOR

Role	Name	Contact Information
Sponsor Study Monitor/Representative Name	(b)(6)	Address as cited for Sponsor Tel: +82 31 8099 1548 E-mail: (b)(6)@cj.net

4. RESPONSIBLE PERSONNEL

Role/Phase	Quality Assurance Unit	Name	Contact Information
Study Director			(b) (4), (b)(6)
Alternative Contact			

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Role/Phase	Quality Assurance Unit	Name	Contact Information
Test Facility Management	(b) (4), (b) (6)		
Test Facility QAU/Lead QA			
Ophthalmology			
Safety Pharmacologist			
Study Pathologist			
Principal Investigators (PI)			
Formulation Analysis (Phase No. 21/300-420AN)[a]	(b) (4), (b)(6)		
T3, T4, TSH hormone measurement (Phase No. 21/300-430AN)[a]			
Test Site QAU			

[a]: Test Site selected by the Study Sponsor in agreement with the Study Director.

Note: Other trained, competent personnel worked on the study (as documented in the raw data).

Appendix 3

5. RESULTS OF THE METHOD VALIDATION

Table 1. Method Validation results (21/300-316AN)

Examined parameters	Results		Acceptance criteria	Compliance
Selectivity	**No interfering** component was observed in the control matrix		Interference in blank samples: ≤ 30% of the LOD	**Passed**
Instrument (reinjection) **repeatability** (n=7)*	RSD% ≤ **1.0%**		RSD%: ≤ 5%	**Passed**
Linear range of the reference item	**0.05 – 10 µg/mL**		Deviation should be ≤15%, except the LOD: ≤20%, the regression coefficient: ≥ 0.99	**Passed**
Limit of Detection of the **HPLC-UV method** (**LOD**)	**0.05 µg/mL of calibration standard**		N/A	**N/A**
Theoretical quantification limit of the **formulation** (**LLOQ**)	**0.05 mg/mL of formulation**		N/A	**N/A**
Mean recovery (accuracy) of the test item from vehicle (distilled water), n=3 (~10 and ~250 mg/mL of test item)	**~10 mg/mL**	**99%**	The measured concentration of the test item compared to the nominal: 100 ± 20%.	**Passed**
	~250 mg/mL	**102%**		**Passed**
Precision (RSD%) of the recovery from formulations from vehicle (distilled water), n=3	**~10 mg/mL**	**0.5%**	The overall precision of the parallel sample preparations per concentration: ≤ 15 RSD%.	**Passed**
	~250 mg/mL	**2.1%**		**Passed**
Stability of the calibration standards in the **autosampler**	**At least 32 hours (105%)**		The area of the stored samples compared to the area of the freshly prepared calibration samples: 100 ± 10%.	**Passed**
Stock solution **stability** at 2 – 8°C	**At least 4 days (99%)**		The area of the stored stock solution compared to the area of fresh solution: 100 ± 10%.	**Passed**

Abbreviations: t.i. test item, RSD: relative standard deviation
*Appropriately cross-validated to other HPLC-UV systems during this study.

Appendix 3

Table 1. continued Method Validation results (21/300-316AN)

Examined parameters	Results		Acceptance criteria	Compliance
Formulation stability in vehicle (distilled water) at room temperature **(RT)** for **8 days (as short term)**	**~10 mg/mL**	**99%**	The measured concentration of the stored formulation compared to the freshly measured: 100 ± 15%	**Passed**
	~250 mg/mL	**103%**		
Formulation stability in vehicle (distilled water) at frozen **(-20°C)** for **6 weeks (as long term)**	**~10 mg/mL**	**105%**		
	~250 mg/mL	**112%**		

Abbreviations: t.i. test item, RSD: relative standard deviation

6. EQUIPMENT AND CHEMICALS

6.1. Test system

HPLC with UV detection: (b) (4)

Balance: (b) (4)

Vortex: (b) (4)

Ultrasonic bath (US):

pH meter:

Water purification system:

Refrigerator:

Freezer:

*Note: During the validation, (b) (4) system was used only. In this study, the method was cross-validated to (b) (4) by measurement of reinjection repeatability, which compliance to (b) (4) system and the validation criteria.

Appendix 3

6.2. Test Item

Information provided by the Sponsor:

Name:	TRP Pro
Alternate identification:	L-tryptophan (TRP Pro) / Tryptophan (TRP Pro)
CAS number:	73-22-3
Batch/Lot number:	(b) (4)
Description:	Light brown granule
Purity:	61.34%
Manufacturer/supplier:	CJ CheilJedang
Manufacturing date:	05 October 2021
Expiry date:	04 October 2023
Storage conditions:	Room temperature (15–25 °C, ≤ 70% relative humidity), protected from light and humidity (tightly closed container)

The test item itself was not used by the Analytical Department of Test Site during the Dose Formulation analysis phase. Instead, the reference item in Section 6.3 was used (e.g. for the preparation of standard solutions).

As agreed with the Sponsor, no correction for purity of the test item was applied for the animal treatment (but tryptophan was measured in this analytical method, therefore the test item concentration was calculated by the purity).

The test item of a suitable chemical purity was provided by the Sponsor. All precautions required in the handling and disposal of the test item were outlined by the Sponsor. The test item was identified on the basis of the information supplied by the Sponsor in the Pharmacy at the Test Facility.

6.3. Reference Item

Information provided by the Supplier (b) (4)

Reference item name:	L-tryptophan
Product number:	L-Tryptophan – BioUltra, ≥ 99.5% (NT)
Product number:	93659
CAS number:	73-22-3
Batch/Lot number:	(b) (4)
Description:	White powder
Purity:	99.9%
Expiry date:	30 November 2025
Storage conditions:	Protected from light and humidity (tightly closed container) at room temperature (15–25 °C)

Correction for purity of the reference item (1.001 as factor) was applied.

6.4. Other Materials

Ultrapure water (H_2O):	ASTM Type I, prepared by Direct-Q 8 UV system
Acetonitrile (ACN):	Super gradient grade, VWR, Batch No.: (b) (4)
H_3PO_4: (ortho-Phosphoric acid)	Reagent grade, 85%, Lach-Ner, Batch No.: (b) (4), (b) (4)
KH_2PO_4: (Potassium dihydrogen phosphate)	Reagent grade, Lach-Ner, Batch No.: (b) (4)

7. METHOD FOR THE ANALYSIS OF TEST ITEM

7.1. Analytical (HPLC-UV) Method

Column:	ACE Excel 5 C18, 150×4.6 mm, 5 µm
Column temperature:	25°C
Mobile Phase (eluent):	Acetonitrile / Buffer = 8/92
	Buffer: 8 mM KH_2PO_4, adjusted with H_3PO_4 to pH 2.9
Elution mode:	Isocratic
Flow:	1 mL/min
Detector (UV):	218 nm
Injection volume:	20 µL
Total run time:	15 min

The active ingredient of the test item was identified according to the retention time of the reference item.

8. PREPARATION OF THE CALIBRATION STANDARDS

8.1. Mixtures and Solutions

8.1.1. Solutions prepared from the reference item

Stock Solution (S_{sol}): (b) (4)

Working solution (W_{sol}): T (b) (4)

Diluent: (b) (4)

Calibration series: (b) (4)

Appendix 3

Table 2. Preparation of calibration series from the test item

Concentration of Cal_{st}	Volume of S_{sol}	Volume of W_{sol}	Final volume of Cal_{st}
µg/mL	mL	mL	mL
Blank	-	-	~2
(b) (4)			

(b) (4)

Table 3. Summary of Standard Curve Parameters with the actual LOD value and the highest deviation of back-calculated values

Analytical occasion	Slope ($mV \times s \times mL \times \mu g^{-1}$)	Intercept ($mV \times s$)	Correlation Coefficient	LOD ($\mu g \times mL^{-1}$)	Highest deviation (%)
26 October 2022	(b) (4)				
19 January 2023					

9. RESULTS OF THE ANALYSIS

The formulation samples (shipped on dry ice) were stored at frozen (-20°) and measured on 26 October 2022 and 19 January 2023, respectively. The samples were thawed and properly homogenised using vortex, and visually checked.

One dilution was prepared from each vial. All samples were diluted into the calibrated range in two steps with diluent (ultrapure water) according to Table 4. After the first dilution step, the dilutions were ultrasonicated for 10 minutes and diluted further. Before the injection, the dilutions were filtered by 0.2 µm PES (polyethersulfone membrane) filter. Each sample was injected twice per vial and analysed by the above detailed HPLC-UV method.

Table 4. Dilution of the formulations into calibrated range

Nominal concentration mg/mL	First dilution step with diluent		Second dilution step with diluent		Total dilution factor
	Amount of TI suspension (g)	Volume of dil. intermediate sample (mL)	Volume of dil. intermediate sample (mL)	Final volume of dil. sample (mL)	
Control	~0.5	100	0.2	5	5000×
50	~0.5	100	0.2	5	5000×
100	~0.5	100	0.2	10	10000×
200	~0.5	100	0.1	10	20000×

The calculation of the test item concentration of the samples was determined based on the validated HPLC-UV method. Results of the analysis are detailed in Table 5.

Appendix 3

Table 5. Measured concentrations of the test formulations

Analytical occasion*	Sample name	Nominal t.i. conc. (mg/mL)	Sample position	Measured t.i. conc. (mg/mL)	Mean t.i. conc. with 95% conf. int. (mg/mL)	Percentage of the nominal conc. (%)	RSD (%)
Preparation: 17 October 2022 Sampling: 18 October 2022 Measurement: 26 October 2022	1Day1 M.1	**0**	M1	N/A	**N/A**	**N/A**	**N/A**
	1Day1 M.2		M2	N/A			
	2Day1T.1	**50**	T1	49.2	**50.4 ± 0.82**	**101**	**1.5**
	2Day1T.2		T2	50.3			
	2Day1 M.1		M1	50.3			
	2Day1 M.2		M2	50.9			
	2Day1 B.1		B1	51.5			
	2Day1 B.2		B2	50.2			
	3Day1 M.1	**100**	M1	104	**103 ± 20.9**	**103**	**2.3**
	3Day1 M.2		M2	101			
	4Day1 T.1	**200**	T1	213	**212 ± 5.4**	**106**	**2.4**
	4Day1 T.2		T2	212			
	4Day1 M.1		M1	219			
	4Day1 M.2		M2	207			
	4Day1 B.1		B1	205			
	4Day1 B.2		B2	214			

*Dates belong to the test item formulations

Abbreviations: t.i. test item; conc. concentration; conf. int. confidence interval; N/A not applicable, RSD: relative standard deviation

Appendix 3

Table 5. continued Measured concentrations of the test formulations

Analytical occasion*	Sample name	Nominal t.i. conc. (mg/mL)	Sample position	Measured t.i. conc. (mg/mL)	Mean a.i. conc. with 95% conf. int. (mg/mL)	Percentage of the nominal conc. (%)	RSD (%)
Preparation: 09 January 2023 Sampling: 09 January 2023 Measurement: 19 January 2023	1Week13M.1	**0**	M1	N/A	**N/A**	**N/A**	**N/A**
	1Week13M.2		M2	N/A			
	2Week13M.1	**50**	M1	48.1	**48.2 ± 2.31**	**96**	**0.5**
	2Week13M.2		M2	48.4			
	3Week13M.1	**100**	M1	100	**102 ± 32.5**	**102**	**3.5**
	3Week13M.2		M2	105			
	4Week13M.1	**200**	M1	213	**210 ± 32.7**	**105**	**1.7**
	4Week13M.2		M2	208			
Preparation: as above Sampling: 17 January 2023 Measurement: 19 January 2023	1Week13+8DaysM.1	**0**	M1	N/A	**N/A**	**N/A**	**N/A**
	1Week13+8DaysM.2		M2	N/A			
	2Week13+8DaysM.1	**50**	M1	47.8	**48.0 ± 2.62**	**96**	**0.6**
	2Week13+8DaysM.2		M2	48.2			
	3Week13+8DaysM.1	**100**	M1	96	**98 ± 35.1**	**98**	**4.0**
	3Week13+8DaysM.2		M2	101			
	4Week13+8DaysM.1	**200**	M1	195	**194 ± 6.6**	**97**	**0.4**
	4Week13+8DaysM.2		M2	194			

*Dates belong to the test item formulations

Abbreviations: t.i. test item; conc. concentration; conf. int. confidence interval; N/A not applicable, RSD: relative standard deviation

10. DISCUSSION AND CONCLUSION

The actual concentrations of the test formulations varied between 96% and 106% of nominal concentrations. The test formulation samples stored at frozen were within the acceptable range of the concentration analysis (100 ± 15% of the measured concentration compared to the nominal concentration). The homogeneity of the 50 and 200 mg/mL of test samples were examined by measurement of the duplicate sampling of top, middle and bottom locations of the formulations on the first analytical occasion. In case of the replicates sent for the homogeneity testing, the relative standard deviation was ≤ 2.4%. The highest relative standard deviation of the replicates was ≤ 4.0%, showing the homogeneity of all the samples. The acceptable criterion of the homogeneity was RSD% ≤ 10%.

On the 2nd formulation analysis, the prepared formulations were sampled twice: firstly, right after the preparation, secondly (b) days after the preparation, applying constant stirring during the (b) days. The test item concentration of the formulations did not show significant differences, both sampling was within the acceptable ranges. Based on the result, the stability of the formulations under continuous stirring for (b) days was confirmed.

The formulation analyses were performed under appropriate analytical conditions.

In summary, the formulation analyses demonstrated homogeneous and accurate sample concentrations were used in the 90-day toxicity study in rats.

11. REGULATORY COMPLIANCE

In order to enable the results of this study phase to meet the requirements for regulatory submission and/or safety assessment, it was performed in compliance with the principles of Good Laboratory Practice Regulations as requested by the Sponsor and specified in the Hungarian Good Laboratory Practice Regulations: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities that correspond to the OECD GLP, ENV/MC/CHEM (98) 17.

These principles are consistent with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community (EMA and National Competent Authorities), the United States (EPA and FDA), and Japan (MHLW, MAFF and METI).

12. COMPUTERIZED SYSTEMS

The following computerized systems used in the study:

Critical Computerized Systems

System Name	Description of Data Collected and/or Analysed
(b) (4)	Test Item receipt
Clarity Chromatography Station v8.4	System control, data acquisition and integration

13. RETENTION AND DISPOSITION OF RECORDS AND SAMPLES

As demanded by the principles of Hungarian GLP and the relevant SOPs of the Test Site, all the phase related documents such as, but not limited to, all raw data, the original Final Phase Report and any amendment(s), shipping documents and correspondence, will be archived for a period of 15 years following the date on which the Final Phase Report will be issued in the Archive of the Test Site (b)(6)). It is the responsibility of the Principal Investigator (PI) to notify the Study Director when the Final Phase Report is archived.

After the retention time at the Test Site has elapsed, the Test Site will contact the Study Director (on behalf of Sponsor) for instructions whether all the archived materials listed above will be offered to the Sponsor or retained for a further period (if agreed by a contract) in the Archive of the Test Site or transferred to external archiving.

All the measured results were within the acceptance criteria; therefore, the remaining samples will be disposed in a safe and proper manner, in accordance with the Study Plan.

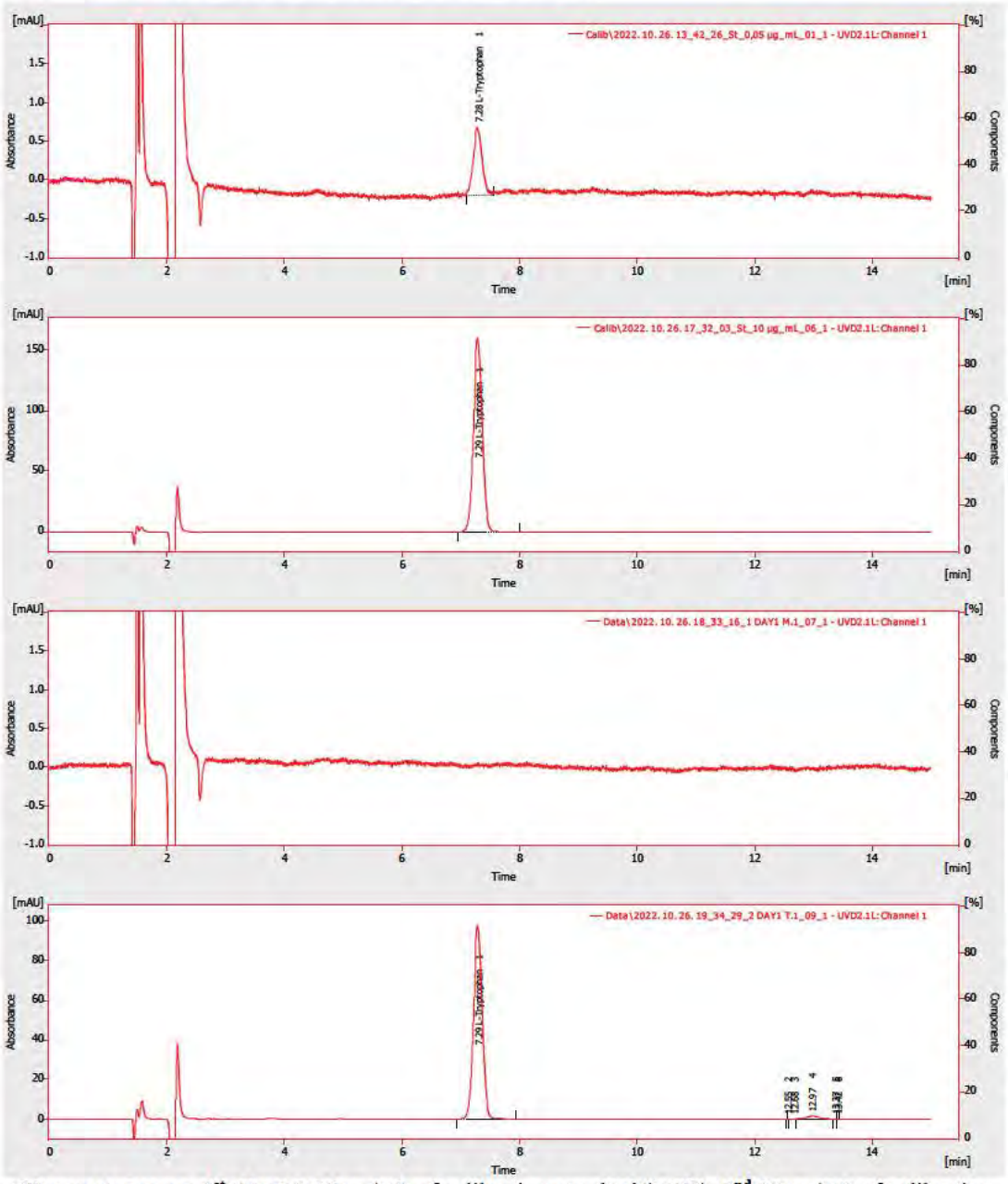
14. DISTRIBUTION OF THE PHASE REPORT

Sponsor / Study Director: 1x PDF-file

Archive of the Test Site: 1x original, bound

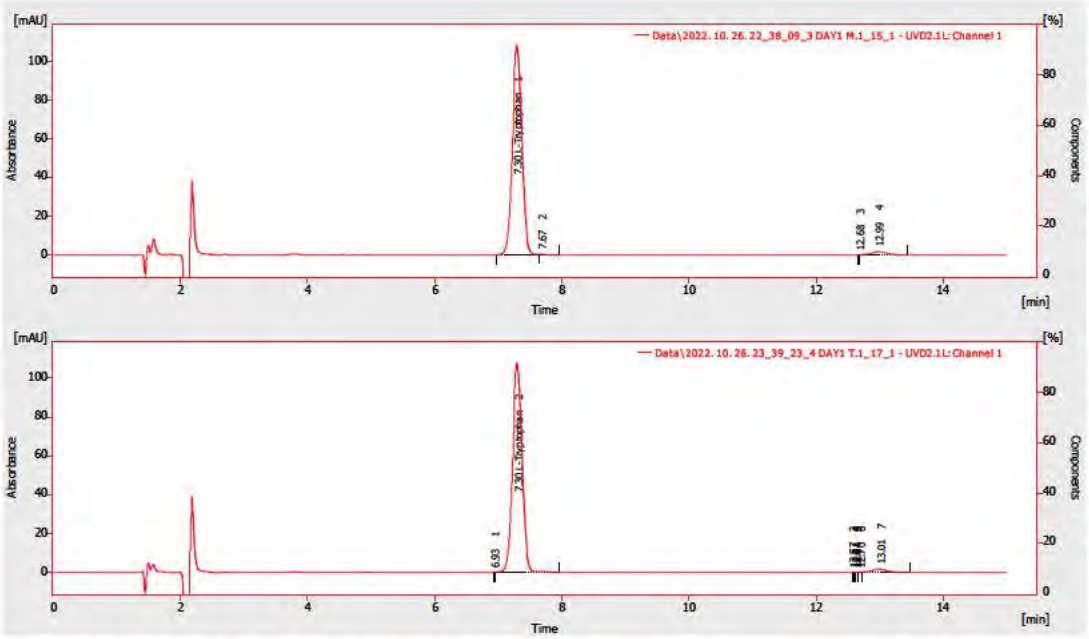
Appendix 3

15. REPRESENTATIVE CHROMATOGRAMS



Chromatograms: 1st (Top) 0.05 µg/mL of calibration standard (LOD), **2nd** 10 µg/mL of calibration standard (ULOQ), **3rd** Control vehicle (distilled water), **4th** 50 mg/mL of formulation (dilution factor: 5000×)

Appendix 3

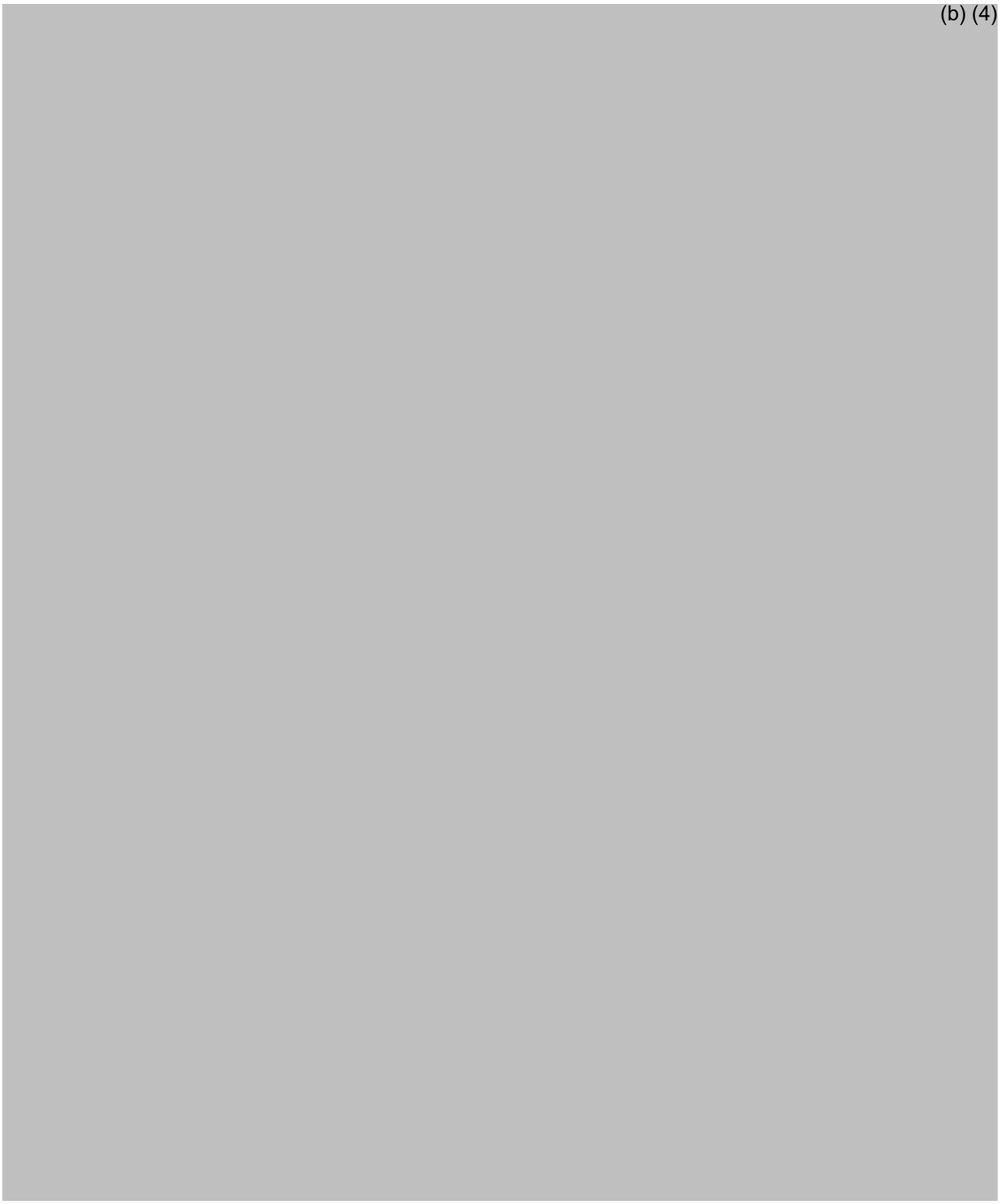


Chromatograms: 5th (Top) 100 mg/mL of formulation (dilution factor: 10000×), **6th** 200 mg/mL of formulation (dilution factor: 20000×)

Appendix 3

COPY OF THE GLP CERTIFICATE OF THE TEST SITE

(b) (4)



INDIVIDUAL DATA EXPLANATION PAGE

All day(s) referenced throughout the outputs generated are study days beginning with Study Day 1, the first day of dosing.

Abbreviations consistent throughout the Individual Tables.

Note:

All of the abbreviations listed on these pages may not be applicable to this report.

GENERAL

Abbreviation	Description	Abbreviation	Description
% Diff	% Difference from control group	N	Number of values included in analysis
FC	Flag Comment	RC	Result comment
Mean	Arithmetic mean	SD	Standard deviation

MORTALITY

Abbreviation	Description	Abbreviation	Description
Path Removal Reason	Pathological Removal Reason	TERM	Terminal euthanasia
REC	Recovery euthanasia		

CLINICAL OBSERVATIONS

Abbreviation	Description	Abbreviation	Description
xH / xM	x hour(s)/minutes postdose[1]	PM_S	In the afternoon on non-dosing days
AM_S	In the morning on non-dosing days	PT	Permanent
DuRx	During dose	VET	Veterinary observation
Pre	Predose	Vet	Clinical observation performed by the Veterinarian

Notes:

- Only animals and occasions with findings are presented.
- "Other (see comment)" on Day 26 for Male No. 1015 (0 mg/kg/day) means "Injury".
- Salivation and associated clinical observations (i.e., pedaling and ploughing) are presented in a specific Appendix.
- "Severity Not Recorded" for salivation 2 hours after dosing on Day 42 for Female No. 2502 (500 mg/kg/day) means that the severity was inadvertently not recorded.

[1] Target times are presented. Actual times are kept in the raw data.

ARENA OBSERVATIONS

Specific Clinical Signs During Arena Observations

Arena: Gait	Normal	
	Demonstrates excessive swaying or lurching without limbs dragging	
	Forelimbs drag, are extended or unable to support weight	
	Hindlimbs show exaggerated or overcompensated movements, drag or appear splayed	
	Tip-toe walk	
Arena: Posture	Appears normal (whether immobile and apparently asleep, awake and immobile, or moving)	
	Hunched or crouched over	
	Lying on side, limbs in air	
	Prostrate [flattened, limb(s) may be spread out]	
Arena: Tremors	Head Limbs Whole body	None
		Slight (barely perceptible)
		Moderate (apparent, but able to perform other activities
		Severe (impairs activity)
Arena: Stereotypical Behavior	Absent (normal)	
	Circling	
	Repetitive mouth movements	
	Stereotypic licking	
	Stereotypic sniffing	
	Stereotypic grooming	
	Stereotypic head movement (head search, weaving or bobbing)	
	Self-mutilation	
	Retropulsion	
	Spontaneous vocalization	
Arena: Alertness	Normal	
	Very low (stuporous, comatose)	
	Low (sluggish, some exploratory movements possible)	
	High (sudden startle, darting or freezing without apparent stimuli)	
	Very high (sudden bouts of running, freezing with spontaneous vocalization)	
Arena: Grooming	Clean and groomed	
	Unkempt (discolored fur, staining around the eyes or nose)	
	Stained by urine and/or feces	
Handling: Body Tone	Normal	
	Flaccid	
	Firm	
Handling: Tactile Reflex	No reaction	
	Minimal response (animal slowly turns towards the stimulus or walks away)	
	Startle response or freezing reaction	
	Exaggerated reaction (jumps at or away from the probe, intense vocalization, attacks or bites)	

Note:

No findings were observed throughout the study, therefore no data have been tabulated.

BODY WEIGHTS

Note:

Terminal body weights (i.e., on Day 91/92 and Day 120) are not presented due to the fasting conditions.

FOOD CONSUMPTION

Abbreviation	Description	Abbreviation	Description
No In Cage	Number of animals per cage	Cons	Consumption

NEUROBEHAVIORAL ASSESSMENT

Abbreviation	Description	Abbreviation	Description
oC	Celsius degree	Pre	Predose
Liquides	Liquid	Refl	Reflex
HC	Home cage	Resp	Response
min	Minute(s)	sec	Second(s)
OF	Open field		

Notes:

- The phase of the observation during which the sign was noted is indicated using the following abbreviations:
  - HC = sign observed in the home cage
  - OF = sign observed while the animal is in the open field
- During the test, rearings are expressed in counts and grip strength is expressed in grams.
- No observation was performed at the end of the recovery period since no findings were reported during the dosing period.

MOTOR ACTIVITY

Note:

No observation was performed at the end of the recovery period since no findings were reported during the dosing period.

OPHTHALMOLOGY OBSERVATIONS

Abbreviation	Description
Persist Pupil	Persistent pupillary

Note:

Only animals and occasions with findings are presented.

CLINICAL PATHOLOGY

Abbreviation	Description	Abbreviation	Description
Cld	Cloudy	NAF	No abnormal findings
CLOT	Sample clotted	Or	Orange
Clr	Clear	Tur	Turbid
DY	Dark yellow	UTDM	Unable to determine, not confirmed by microscopy
LY	Light yellow		

HEMATOLOGY AND COAGULATION VALUES/BLOOD SMEARS OBSERVATIONS

Hematology and Coagulation

Abbreviation	Description	Abbreviation	Description
^x/L	10^x/L	MCV	Mean corpuscular volume
APTT	Activated partial thromboplastin time	MONO	Monocytes
BASO	Basophils	MPV	Mean platelet volume
EOS	Eosinophils	NEUT	Neutrophils
FIB	Fibrinogen concentration	PLT	Platelets
HCT	Hematocrit	PT	Prothrombin time
HGB	Hemoglobin	RBC	Red blood cells
LUC	Large unstained cells	RDWG	Red blood cell distribution width gated
LYMPH	Lymphocytes	RETIC	Reticulocytes
MCH	Mean corpuscular hemoglobin	WBC	White blood cells
MCHC	Mean corpuscular hemoglobin concentration		

Cell Morphology

Abbreviation	Description	Abbreviation	Description
1+	Minimal	ROULEAUX	Rouleaux formation
4+	Marked	WBC MORPH	White blood cell morphology
POLY	Polychromasia		

CLINICAL CHEMISTRY VALUES

Abbreviation	Description	Abbreviation	Description
A/G	Albumin/Globulin	GLUC	Glucose
ALB	Albumin	HDL	High Density Lipoprotein
ALP	Alkaline phosphatase	K	Potassium
ALT	Alanine aminotransferase	LDL	Low Density Lipoprotein
AST	Aspartate aminotransferase	NA	Sodium
BILEAC	Bile acids	PHOS	Phosphorus
CA	Calcium	TBIL	Total bilirubin
CHOL	Cholesterol	TPROT	Total protein
CL	Chloride	TRIG	Triglycerides
CREAT	Creatinine	UREA	Urea nitrogen
GGT	Gamma glutamyltransferase	umol	Micromol
GLOB	Globulin		

URINE VALUES

Abbreviation	Description	Abbreviation	Description
BIL	Urine bilirubin	mOsm/kg	mOsmol/kg
BLD	Urine blood	NIT	Urine nitrite
CLARITY	Urine clarity	OSMLTY	Urine osmolality
COLOR	Urine color	PROT	Urine protein
GLUC	Urine glucose	SPECIFIC GRAVITY	Urine specific gravity
KET	Urine ketones	VOLUME	Urine volume

Microscopic Examination (Sediment)

Abbreviation	Parameter	Abbreviation	Parameter
URINE MICROSCOPIC	Urine microscopic	OTHER	Urine other
EPIC	Urine epithelial cells	SPERM	Urine spermatozoa
HPF	High power field	BACT	Urine bacteria
LPF	Low power field		
Crystals			
AMPH CRYS	Amorphous	CAOX CRYS	Calcium oxalate
CACO CRYS	Calcium carbonate	TPHOS CRYS	Triple phosphate

Scores for qualitative or semi-quantitative estimations

Clarity (Turbidity):	Clr (Clear)	Cld (Cloudy)	Tur (Turbid)		
pH: 5.0 to 9.0 (measuring range). Values above 9.0 are recorded by the instrument as 9.0.					
Protein: (g/L)	Neg (NEGATIVE)	1+ (TRACES)	2+ (0.3)	3+ (1.0)	4+ (≥ 3.0)
Glucose: (mmol/L)	Neg (NEGATIVE)	1+ (5.5)	2+ (14)	3+ (28)	4+ (≥ 55)
Ketones: (mmol/L)	Neg (NEGATIVE)	1+ (TRACES)	2+ (1.5)	3+ (3.9)	4+ (≥ 7.8)
Bilirubin:	Neg (NEGATIVE)	1+ (SMALL)	2+ (MODERATE)	3+ (LARGE)	
Blood:	Neg (NEGATIVE)	1+ (TRACES)	2+ (SMALL)	3+ (MODERATE)	4+ (LARGE)
Nitrite:	Neg (NEGATIVE)	Pos (POSITIVE)			
Casts (lpf)	1+ 1-2	2+ 3-7	3+ 8-15	4+ > 15	
WBC (hpf)	1+ 1-5	2+ 6-20	3+ 21-50	4+ > 50	
RBC (hpf)	1+ 1-5	2+ 6-20	3+ 21-50	4+ > 50	
Crystals (hpf)	1+ 1-5	2+ 6-10	3+ 11-20	4+ > 20	
Bacteria Cysto/Catheter (hpf)	1+ 1-2	2+ 3-9	3+ 10-20	4+ > 20	
Bacteria/Other Non-Cysto/Catheter (hpf)	1+ 1-25%	2+ 26-50%	3+ 51-75%	4+ > 75%	

ESTROUS CYCLE

Abbreviation	Description	Abbreviation	Description
D	Di-estrus	M	Met-estrus
E	Estrus	P	Pro-estrus

Note:

At the end of the dosing period, main females were euthanized on Day 91 or Day 92 (the first 5/group on Day 91, the last 5/group on Day 92). For practical purpose, results are presented under the same occasion (Day 91 or Day 92).

SPERM COUNT AND MOTILITY

Notes:

- At the end of the dosing period, main males were euthanized on Day 91 or Day 92. For comparison purpose, results are presented together.
- Male No. 4001 (2000 mg/kg/day) showed atypical results due to unilateral diffuse atrophy not considered to be related to the administration of the test item. Data from this animal were therefore excluded from the calculation of mean and standard deviation.

SPERM MORPHOLOGY

Abbreviation	Description
Abnormal Sperm Combo	Abnormal sperm combined

Note:

Male No. 4001 (2000 mg/kg/day) showed atypical results due to unilateral diffuse atrophy not considered to be related to the administration of the test item. Data from this animal were therefore excluded from the calculation of mean and standard deviation.

ORGAN WEIGHTS

Abbreviation	Description	Abbreviation	Description
%br	Relative to brain weights	Seminal Ves	Seminal vesicle
%bw	Relative to body weights	Wt	Weight
Coagul or Coagulating	Coagulating gland		

Note:

At the end of the dosing period, main animals were euthanized on Day 91 or Day 92 (the first 5/group/sex on Day 91, the last 5/group/sex on Day 92). For comparison purpose, results are presented under the same occasion (Day 91/92).

MACROSCOPIC/MICROSCOPIC OBSERVATIONS

Abbreviation	Description	Abbreviation	Description
?	Questionable	H	Histopathology
C	Clinical observation	M	Mass
E	Excluded	MPF	Major pathological finding
G	Gross pathology	NBF	Neutral buffered formalin
GALT	Gut-associated lymphoid tissue	TGL	Trackable gross lesion

HISTORICAL CONTROL DATA

Notes:

- Values compiled from undosed and control Han Wistar rats in previous studies.
- The historical control data presented in the Appendix are not subject to Quality Assurance audit.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 4

24-Feb-2023 08:42:10

Individual Mortality

(b) (4)

Sex: Male Day(s): - Relative to Start Date

0 mg/kg /day Group 1	Day of Death	Removal Date	Path Removal Reason
1001	91	16-Jan-2023	TERM
1002	91	16-Jan-2023	TERM
1003	91	16-Jan-2023	TERM
1004	91	16-Jan-2023	TERM
1005	91	16-Jan-2023	TERM
1006	92	17-Jan-2023	TERM
1007	92	17-Jan-2023	TERM
1008	92	17-Jan-2023	TERM
1009	92	17-Jan-2023	TERM
1010	92	17-Jan-2023	TERM
1011	120	14-Feb-2023	REC
1012	120	14-Feb-2023	REC
1013	120	14-Feb-2023	REC
1014	120	14-Feb-2023	REC
1015	120	14-Feb-2023	REC

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 4

24-Feb-2023 08:42:10

Individual Mortality

(b) (4)

Sex: Male Day(s): - Relative to Start Date

500 mg/kg /day Group 2	Day of Death	Removal Date	Path Removal Reason
2001	91	16-Jan-2023	TERM
2002	91	16-Jan-2023	TERM
2003	91	16-Jan-2023	TERM
2004	91	16-Jan-2023	TERM
2005	91	16-Jan-2023	TERM
2006	92	17-Jan-2023	TERM
2007	92	17-Jan-2023	TERM
2008	92	17-Jan-2023	TERM
2009	92	17-Jan-2023	TERM
2010	92	17-Jan-2023	TERM

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 4

24-Feb-2023 08:42:10

Individual Mortality

(b) (4)

Sex: Male Day(s): - Relative to Start Date

1000 mg/kg /day Group 3	Day of Death	Removal Date	Path Removal Reason
3001	91	16-Jan-2023	TERM
3002	91	16-Jan-2023	TERM
3003	91	16-Jan-2023	TERM
3004	91	16-Jan-2023	TERM
3005	91	16-Jan-2023	TERM
3006	92	17-Jan-2023	TERM
3007	92	17-Jan-2023	TERM
3008	92	17-Jan-2023	TERM
3009	92	17-Jan-2023	TERM
3010	92	17-Jan-2023	TERM

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 4

24-Feb-2023 08:42:10

Individual Mortality

(b) (4)

Sex: Male Day(s): - Relative to Start Date

2000 mg/kg /day Group 4	Day of Death	Removal Date	Path Removal Reason
4001	91	16-Jan-2023	TERM
4002	91	16-Jan-2023	TERM
4003	91	16-Jan-2023	TERM
4004	91	16-Jan-2023	TERM
4005	91	16-Jan-2023	TERM
4006	92	17-Jan-2023	TERM
4007	92	17-Jan-2023	TERM
4008	92	17-Jan-2023	TERM
4009	92	17-Jan-2023	TERM
4010	92	17-Jan-2023	TERM
4011	120	14-Feb-2023	REC
4012	120	14-Feb-2023	REC
4013	120	14-Feb-2023	REC
4014	120	14-Feb-2023	REC
4015	120	14-Feb-2023	REC

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 4

24-Feb-2023 08:42:10

Individual Mortality

(b) (4)

Sex: Female Day(s): - Relative to Start Date

0 mg/kg /day Group 1	Day of Death	Removal Date	Path Removal Reason
1501	91	16-Jan-2023	TERM
1502	91	16-Jan-2023	TERM
1503	91	16-Jan-2023	TERM
1504	91	16-Jan-2023	TERM
1505	91	16-Jan-2023	TERM
1506	92	17-Jan-2023	TERM
1507	92	17-Jan-2023	TERM
1508	92	17-Jan-2023	TERM
1509	92	17-Jan-2023	TERM
1510	92	17-Jan-2023	TERM
1511	120	14-Feb-2023	REC
1512	120	14-Feb-2023	REC
1513	120	14-Feb-2023	REC
1514	120	14-Feb-2023	REC
1515	120	14-Feb-2023	REC

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 4

24-Feb-2023 08:42:10

Individual Mortality

(b) (4)

Sex: Female Day(s): - Relative to Start Date

500 mg/kg /day Group 2	Day of Death	Removal Date	Path Removal Reason
2501	91	16-Jan-2023	TERM
2502	91	16-Jan-2023	TERM
2503	91	16-Jan-2023	TERM
2504	91	16-Jan-2023	TERM
2505	91	16-Jan-2023	TERM
2506	92	17-Jan-2023	TERM
2507	92	17-Jan-2023	TERM
2508	92	17-Jan-2023	TERM
2509	92	17-Jan-2023	TERM
2510	92	17-Jan-2023	TERM

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 4

24-Feb-2023 08:42:10

Individual Mortality

(b) (4)

Sex: Female Day(s): - Relative to Start Date

1000 mg/kg /day Group 3	Day of Death	Removal Date	Path Removal Reason
3501	91	16-Jan-2023	TERM
3502	91	16-Jan-2023	TERM
3503	91	16-Jan-2023	TERM
3504	91	16-Jan-2023	TERM
3505	91	16-Jan-2023	TERM
3506	92	17-Jan-2023	TERM
3507	92	17-Jan-2023	TERM
3508	92	17-Jan-2023	TERM
3509	92	17-Jan-2023	TERM
3510	92	17-Jan-2023	TERM

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 4

24-Feb-2023 08:42:10

Individual Mortality

(b) (4)

Sex: Female Day(s): - Relative to Start Date

2000 mg/kg /day Group 4	Day of Death	Removal Date	Path Removal Reason
4501	91	16-Jan-2023	TERM
4502	91	16-Jan-2023	TERM
4503	91	16-Jan-2023	TERM
4504	91	16-Jan-2023	TERM
4505	91	16-Jan-2023	TERM
4506	92	17-Jan-2023	TERM
4507	92	17-Jan-2023	TERM
4508	92	17-Jan-2023	TERM
4509	92	17-Jan-2023	TERM
4510	92	17-Jan-2023	TERM
4511	120	14-Feb-2023	REC
4512	120	14-Feb-2023	REC
4513	120	14-Feb-2023	REC
4514	120	14-Feb-2023	REC
4515	120	14-Feb-2023	REC

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 5

16-Mar-2023 09:27:00

Individual Clinical Observations

(b) (4)

0 mg/kg /day Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		26	28 Vet	29	30 Vet	32 Vet	35 Vet	36
1001	Teeth, Broken	.	.	.	.	.	.	.
1003	Discharge, Color, Eye, Left, Red	.	.	.	.	.	.	.
1013	Skin, Discolored, Periorbital, Left, Red	.	.	.	.	.	.	.
1015 !	Skin Lesion (VET), Forelimb, Right, Slight, Dry	.	.	.	X	X	X	.
	Skin Lesion (VET), Forelimb, Right, Slight, Sticky	.	X	.	.	.	.	.
	Skin, Scab, Dorsal Cervical	.	.	X	.	.	.	X
	Skin, Scab, Forelimb, Right	.	.	.	.	.	.	.
	Other (see comment), Forepaw, Right	X	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 5

16-Mar-2023 09:27:00

Individual Clinical Observations

(b) (4)

0 mg/kg /day Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		39 Vet	64	70 2H	71	71 Pre	85 4H	86 Pre
1001	Teeth, Broken	.	X	.	X	.	.	.
1003	Discharge, Color, Eye, Left, Red	.	.	.	.	.	X	X
1013	Skin, Discolored, Periorbital, Left, Red	.	.	X	.	X	.	.
1015	Skin Lesion (VET), Forelimb, Right, Slight, Dry	.	.	.	.	.	.	.
	Skin Lesion (VET), Forelimb, Right, Slight, Sticky	.	.	.	.	.	.	.
	Skin, Scab, Dorsal Cervical	.	.	.	.	.	.	.
	Skin, Scab, Forelimb, Right	X	.	.	.	.	.	.
	Other (see comment), Forepaw, Right	.	.	.	.	.	.	.

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 5

16-Mar-2023 09:27:00

Individual Clinical Observations

(b) (4)

0 mg/kg /day Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		86 2H	87 Pre					
1001	Teeth, Broken	.	.					
1003	Discharge, Color, Eye, Left, Red	X	X					
1013	Skin, Discolored, Periorbital, Left, Red	.	.					
1015	Skin Lesion (VET), Forelimb, Right, Slight, Dry	.	.					
	Skin Lesion (VET), Forelimb, Right, Slight, Sticky	.	.					
	Skin, Scab, Dorsal Cervical	.	.					
	Skin, Scab, Forelimb, Right	.	.					
	Other (see comment), Forepaw, Right	.	.					

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 5

20-Feb-2023 08:38:33

Individual Clinical Observations

(b) (4)

500 mg/kg /day Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		8	16	22	29	36	43 Pre	50
2008	Fur, Staining, Dorsal Thoracic, Red	.	.	.	.	X	X	X
	Skin, Scab, Dorsal Thoracic	X	X	X	X	X	X	X
2009	Fur, Staining, Dorsal Thoracic, Red	.	.	.	.	.	.	X
	Fur, Thin Cover, Abdominal	.	.	.	.	.	.	.
	Skin, Scab, Dorsal Thoracic	.	.	.	.	.	.	X

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 5

20-Feb-2023 08:38:33

Individual Clinical Observations

(b) (4)

500 mg/kg /day Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		57	64	71	78	84	90	
2008	Fur, Staining, Dorsal Thoracic, Red	X	X	X	X	X	.	
	Skin, Scab, Dorsal Thoracic	X	X	X	X	X	.	
2009	Fur, Staining, Dorsal Thoracic, Red	X	X	.	.	.	.	
	Fur, Thin Cover, Abdominal	.	.	X	X	X	X	
	Skin, Scab, Dorsal Thoracic	X	X	.	.	.	.	

X=Present

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 5

20-Feb-2023 08:38:33

Individual Clinical Observations

(b) (4)

1000 mg/kg /day Group 3 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		71	78	84	90			
3006	Tail, Bent (PT)	X	X	X	X			

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 5

20-Feb-2023 08:38:34

Individual Clinical Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		71	78	84	90			
4001	Fur, Thin Cover, Abdominal	.	X	X	X			
4002	Fur, Thin Cover, Abdominal	.	.	.	X			
4003	Fur, Thin Cover, Dorsal Thoracic	X	X	X	X			

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 5

20-Feb-2023 08:38:04

Individual Clinical Observations

(b) (4)

0 mg/kg /day Group 1 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-7 PM_S	1	8	98 AM_S	105		
1511	Fur, Thin Cover, Face	.	.	.	X	X		
1512	Fur, Thin Cover, Face	.	.	.	X	X		
	Skin, Scab, Face	.	.	.	X	.		
1513	Fur, Thin Cover, Lumbar	.	.	X	.	.		
	Skin, Scab, Lumbar	X	X	.	.	.		

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 5

20-Feb-2023 08:38:04

Individual Clinical Observations

(b) (4)

500 mg/kg /day Group 2 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		78						
2504	Fur, Staining, Dorsal Cervical, Red	X						
2505	Fur, Staining, Dorsal Cervical, Red	X						

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 5

20-Feb-2023 08:38:33

Individual Clinical Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		57	64	71	78	84	90	98 AM_S
4507	Fur, Thin Cover, Forepaw, Left	.	.	.	.	X	X	.
	Fur, Thin Cover, Forepaw, Right	.	.	.	.	X	X	.
4513	Fur, Thin Cover, Dorsal Cervical	.	.	.	.	X	X	X
	Fur, Thin Cover, Dorsal Thoracic	.	.	.	.	X	X	X
	Fur, Thin Cover, Lumbar	X	X	X	X	.	.	.
4515	Fur, Thin Cover, Dorsal Cervical	.	.	.	.	X	X	X
	Fur, Thin Cover, Forepaw, Left	.	.	.	X	.	.	.
	Fur, Thin Cover, Forepaw, Right	.	.	.	X	.	.	.

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 5

20-Feb-2023 08:38:33

Individual Clinical Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		105	112 AM_S	119 AM_S				
4507	Fur, Thin Cover, Forepaw, Left	.	.	.				
	Fur, Thin Cover, Forepaw, Right	.	.	.				
4513	Fur, Thin Cover, Dorsal Cervical	X	X	X				
	Fur, Thin Cover, Dorsal Thoracic	X	X	X				
	Fur, Thin Cover, Lumbar	.	.	.				
4515	Fur, Thin Cover, Dorsal Cervical	X	X	X				
	Fur, Thin Cover, Forepaw, Left	.	.	.				
	Fur, Thin Cover, Forepaw, Right	.	.	.				

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 6

20-Feb-2023 08:45:34

Individual Salivation and Associated Clinical Observations

(b) (4)

500 mg/kg /day Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		24 5M	45 5M	73 5M				
2001	Salivation, Slight	.	X	X				
	Pedaling	.	.	X				
2002	Salivation, Slight	.	X	.				
	Ploughing	.	X	.				
2003	Salivation, Slight	.	X	X				
	Pedaling	.	X	.				
	Ploughing	.	X	X				
2004	Salivation, Slight	.	.	X				
	Ploughing	.	.	X				
2005	Salivation, Moderate	.	.	X				
	Salivation, Slight	.	X	.				
	Pedaling	.	X	.				
	Ploughing	.	X	.				
2007	Salivation, Slight	.	.	X				
2008	Salivation, Severe	.	.	X				
	Salivation, Slight	.	X	.				
	Pedaling	.	.	X				
	Ploughing	.	.	X				
2009	Salivation, Moderate	.	.	X				
	Salivation, Slight	.	X	.				
	Ploughing	.	.	X				
2010	Salivation, Slight	X	.	.				

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 6

20-Feb-2023 08:45:34

Individual Salivation and Associated Clinical Observations

(b) (4)

1000 mg/kg /day Group 3 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		24 5M	42 DuRx	43 Pre	43 3H	45 5M	73 5M	
3001	Salivation, Moderate	.	.	.	.	X	.	
	Salivation, Severe	.	.	.	.	.	X	
	Salivation, Slight	X	.	.	.	.	.	
	Pedaling	.	.	.	.	X	X	
	Ploughing	.	.	.	.	X	X	
3002	Salivation, Moderate	X	.	.	.	X	.	
	Salivation, Severe	.	.	.	.	.	X	
	Salivation, Slight	.	X	X	X	.	.	
	Pedaling	.	.	.	.	.	X	
	Ploughing	.	.	.	.	X	X	
3003	Salivation, Moderate	.	.	.	.	X	X	
	Salivation, Slight	X	.	.	.	.	.	
	Pedaling	.	.	.	.	X	.	
	Ploughing	.	.	.	.	X	X	
3004	Salivation, Moderate	X	.	.	.	X	.	
	Salivation, Slight	.	.	X	.	.	X	
	Pedaling	.	.	.	.	X	X	
	Ploughing	.	.	.	.	X	.	
3005	Salivation, Moderate	X	.	.	.	.	.	
	Salivation, Slight	.	.	.	.	X	X	
	Pedaling	.	.	.	.	.	X	
	Ploughing	.	.	.	.	X	.	
3006	Salivation, Moderate	.	.	.	.	.	X	
	Salivation, Slight	X	.	.	.	X	.	

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 6

20-Feb-2023 08:45:34

Individual Salivation and Associated Clinical Observations

(b) (4)

1000 mg/kg /day Group 3 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		24 5M	42 DuRx	43 Pre	43 3H	45 5M	73 5M	
3006	Ploughing	.	.	.	.	.	X	
3007	Salivation, Severe	.	.	.	.	.	X	
	Salivation, Slight	.	.	.	.	X	.	
	Pedaling	.	.	.	.	.	X	
	Ploughing	.	.	.	.	.	X	
3008	Salivation, Slight	.	.	.	.	.	X	
3009	Salivation, Slight	.	.	.	.	.	X	
3010	Salivation, Moderate	.	.	.	.	X	.	
	Salivation, Slight	X	.	.	.	.	X	

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 6

20-Feb-2023 08:45:34

Individual Salivation and Associated Clinical Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		17 5M	24 5M	42 DuRx	45 5M	73 5M	73 1H	
4001	Salivation, Moderate	.	.	.	.	X	.	
	Salivation, Slight	.	X	.	X	.	.	
	Pedaling	.	.	.	X	X	.	
	Ploughing	X	.	.	X	X	.	
4002	Salivation, Moderate	X	.	.	.	X	.	
	Salivation, Slight	.	X	.	X	.	X	
	Pedaling	X	.	.	.	X	.	
	Ploughing	X	.	.	X	X	.	
4003	Salivation, Moderate	X	.	.	X	X	.	
	Salivation, Slight	.	X	.	.	.	.	
	Pedaling	X	.	.	X	X	.	
	Ploughing	X	.	.	X	X	.	
4004	Salivation, Moderate	.	X	.	.	.	.	
	Salivation, Severe	.	.	.	X	.	.	
	Salivation, Slight	X	.	.	.	X	.	
	Pedaling	.	.	.	X	X	.	
	Ploughing	X	.	.	X	X	.	
4005	Salivation, Moderate	X	X	.	X	.	.	
	Salivation, Severe	.	.	.	.	X	.	
	Pedaling	.	.	.	X	X	.	
	Ploughing	X	.	.	X	X	.	
4006	Salivation, Moderate	.	X	.	.	X	.	
	Salivation, Severe	.	.	.	X	.	.	
	Salivation, Slight	X	.	X	.	.	.	

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 6

20-Feb-2023 08:45:34

Individual Salivation and Associated Clinical Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		17 5M	24 5M	42 DuRx	45 5M	73 5M	73 1H	
4006	Pedaling	.	.	.	X	X	.	
	Ploughing	X	.	.	.	X	.	
4007	Salivation, Moderate	X	.	.	.	X	.	
	Salivation, Severe	.	.	.	X	.	.	
	Salivation, Slight	.	X	.	.	.	.	
	Pedaling	X	.	.	X	X	.	
	Ploughing	X	.	.	X	X	.	
4008	Salivation, Slight	.	X	.	X	.	.	
4009	Salivation, Moderate	.	.	.	X	.	.	
	Salivation, Severe	.	.	.	.	X	.	
	Salivation, Slight	.	.	X	.	.	.	
	Pedaling	X	.	.	X	X	.	
	Ploughing	X	.	.	X	X	.	
4010	Salivation, Moderate	.	.	.	X	X	.	
	Salivation, Slight	X	X	X	.	.	.	
	Pedaling	.	.	.	X	.	.	
	Ploughing	X	.	.	X	X	.	
4011	Salivation, Moderate	.	.	.	X	X	.	
	Pedaling	X	.	.	X	X	.	
	Ploughing	X	.	.	X	.	.	
4012	Salivation, Moderate	.	.	.	X	X	.	
	Salivation, Slight	X	X	.	.	.	.	
	Pedaling	X	.	.	X	X	.	
	Ploughing	X	.	.	X	X	.	

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 6

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Individual Salivation and Associated Clinical Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		17 5M	24 5M	42 DuRx	45 5M	73 5M	73 1H	
4013	Salivation, Moderate	X	.	.	X	X	.	
	Salivation, Slight	.	X	.	.	.	.	
	Pedaling	X	.	.	X	X	.	
	Ploughing	X	.	.	X	X	.	
4014	Salivation, Moderate	X	.	.	X	.	.	
	Salivation, Slight	.	.	.	.	X	.	
	Pedaling	X	.	.	X	X	.	
	Ploughing	X	.	.	X	X	.	
4015	Salivation, Moderate	.	X	.	X	X	.	
	Pedaling	.	.	.	X	X	.	
	Ploughing	X	.	.	.	X	.	

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 6

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Individual Salivation and Associated Clinical Observations

(b) (4)

500 mg/kg /day Group 2 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		24 5M	42 DuRx	42 2H	45 5M	73 5M		
2501	Salivation, Slight	.	.	.	.	X		
	Pedaling	.	.	.	.	X		
	Ploughing	.	.	.	X	X		
2502	Salivation, Severity Not Recorded	.	.	X	.	.		
	Salivation, Slight	.	X	.	.	X		
	Pedaling	.	.	.	.	X		
2503	Salivation, Slight	.	.	.	X	X		
	Pedaling	.	.	.	.	X		
	Ploughing	.	.	.	X	.		
2504	Salivation, Slight	.	.	.	.	X		
	Pedaling	.	.	.	.	X		
2505	Salivation, Moderate	.	.	.	.	X		
	Salivation, Slight	.	.	.	X	.		
	Pedaling	.	.	.	.	X		
	Ploughing	.	.	.	X	X		
2506	Salivation, Moderate	.	.	.	.	X		
	Salivation, Slight	X	.	.	X	.		
	Pedaling	.	.	.	X	X		
	Ploughing	.	.	.	X	X		
2507	Salivation, Slight	.	.	.	X	X		
	Ploughing	.	.	.	.	X		
2508	Salivation, Slight	X	.	.	X	X		
	Pedaling	.	.	.	.	X		
2509	Salivation, Moderate	X	.	.	.	X		

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 6

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Individual Salivation and Associated Clinical Observations

(b) (4)

500 mg/kg /day Group 2 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		24 5M	42 DuRx	42 2H	45 5M	73 5M		
2509	Salivation, Slight	.	X	.	X	.		
	Pedaling	.	.	.	X	X		
	Ploughing	.	.	.	X	X		
2510	Salivation, Slight	X	.	.	X	X		
	Pedaling	.	.	.	X	X		

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 6

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Individual Salivation and Associated Clinical Observations

(b) (4)

1000 mg/kg /day Group 3 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		17 5M	24 5M	42 DuRx	43 Pre	43 3H	45 5M	73 5M
3501	Salivation, Moderate	.	X	.	.	.	.	.
	Salivation, Slight	.	.	X	X	.	X	X
	Pedaling	.	.	.	.	.	X	X
	Ploughing	.	.	.	.	.	X	X
3502	Salivation, Moderate	X	.	.	.	.	.	X
	Salivation, Slight	.	X	X	.	.	X	.
	Pedaling	.	.	.	.	.	.	X
	Ploughing	X	.	.	.	.	.	X
3503	Salivation, Moderate	.	.	.	.	.	X	X
	Salivation, Slight	.	X	.	.	.	.	.
	Pedaling	.	.	.	.	.	.	X
	Ploughing	.	.	.	.	.	X	X
3504	Salivation, Moderate	.	.	.	.	.	.	X
	Salivation, Slight	.	X	.	.	.	X	.
	Pedaling	.	.	.	.	.	X	X
	Ploughing	.	.	.	.	.	X	X
3505	Salivation, Moderate	.	.	.	.	.	X	X
	Pedaling	.	.	.	.	.	.	X
	Ploughing	.	.	.	.	.	.	X
3506	Salivation, Moderate	X	X	.	.	.	X	.
	Salivation, Severe	.	.	.	.	.	.	X
	Pedaling	.	.	.	.	.	X	X
	Ploughing	.	.	.	.	.	X	X
3507	Salivation, Moderate	X	.	.	.	.	X	X

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Salivation and Associated Clinical Observations

(b) (4)

1000 mg/kg /day Group 3 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		17 5M	24 5M	42 DuRx	43 Pre	43 3H	45 5M	73 5M
3507	Salivation, Severe	.	X	.	.	.	.	.
	Salivation, Slight	.	.	.	X	X	.	.
	Pedaling	.	.	.	.	.	X	X
	Ploughing	X	.	.	.	.	.	X
3508	Salivation, Moderate	.	.	.	.	.	.	X
	Pedaling	.	.	.	.	.	.	X
	Ploughing	.	.	.	.	.	.	X
3509	Salivation, Slight	.	.	.	.	.	X	X
	Ploughing	.	.	.	.	.	X	X
3510	Salivation, Moderate	.	.	.	.	.	X	X
	Salivation, Slight	.	X	.	.	.	.	.
	Pedaling	.	.	.	.	.	.	X
	Ploughing	.	.	.	.	.	.	X

X=Present

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Individual Salivation and Associated Clinical Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		17 5M	24 5M	42 DuRx	43 Pre	43 3H	45 5M	73 5M
4501	Salivation, Moderate	X	.	.	.	.	X	X
	Salivation, Slight	.	X	.	.	.	.	.
	Pedaling	.	.	.	.	.	X	X
	Ploughing	X	.	.	.	.	X	X
4502	Salivation, Moderate	X	.	.	.	.	X	.
	Salivation, Slight	.	X	.	.	.	.	X
	Ploughing	X	.	.	.	.	.	.
4503	Salivation, Moderate	X	.	.	.	.	X	.
	Salivation, Slight	.	.	.	.	.	.	X
	Pedaling	.	.	.	.	.	X	X
	Ploughing	X	.	.	.	.	X	.
4504	Salivation, Moderate	X	.	.	.	.	X	.
	Salivation, Slight	.	.	.	.	.	.	X
	Pedaling	.	.	.	.	.	X	X
	Ploughing	X	.	.	.	.	X	X
4505	Salivation, Moderate	X	.	.	.	.	X	.
	Salivation, Severe	.	.	.	.	.	.	X
	Salivation, Slight	.	X	X	.	.	.	.
	Pedaling	.	.	.	.	.	X	X
	Ploughing	X	.	.	.	.	X	X
4506	Salivation, Moderate	.	.	.	.	.	X	X
	Salivation, Severe	X	.	.	.	.	.	.
	Salivation, Slight	.	.	X	X	X	.	.
	Pedaling	X	.	.	.	.	X	X

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Salivation and Associated Clinical Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		17 5M	24 5M	42 DuRx	43 Pre	43 3H	45 5M	73 5M
4506	Ploughing	X	.	.	.	.	.	X
4507	Salivation, Slight	X	X	.	.	.	X	X
	Pedaling	X	.	.	.	.	.	X
	Ploughing	X	.	.	.	.	X	X
4508	Salivation, Moderate	X	.	.	.	.	.	.
	Salivation, Severe	.	.	.	.	.	.	X
	Salivation, Slight	.	X	X	.	.	X	.
	Pedaling	X	.	.	.	.	.	X
	Ploughing	X	.	.	.	.	X	X
4509	Salivation, Moderate	X	.	.	.	.	X	.
	Salivation, Slight	.	X	X	.	.	.	X
	Pedaling	.	.	.	.	.	.	X
	Ploughing	X	.	.	.	.	.	X
4510	Salivation, Moderate	X	.	.	.	.	X	.
	Salivation, Slight	.	.	.	.	.	.	X
	Pedaling	.	.	.	.	.	X	X
	Ploughing	X	.	.	.	.	X	X
4511	Salivation, Moderate	.	.	.	.	.	.	X
	Salivation, Slight	.	X	.	.	.	X	.
	Pedaling	X	.	.	.	.	.	X
	Ploughing	X	.	.	.	.	X	X
4512	Salivation, Moderate	.	X	.	.	.	X	.
	Salivation, Severe	.	.	.	.	.	.	X
	Salivation, Slight	X	.	.	.	.	.	.

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Salivation and Associated Clinical Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		17 5M	24 5M	42 DuRx	43 Pre	43 3H	45 5M	73 5M
4512	Pedaling	.	.	.	.	.	X	X
	Ploughing	X	.	.	.	.	X	X
4513	Salivation, Moderate	.	.	.	.	.	X	X
	Salivation, Slight	X	X	.	.	X	.	.
	Pedaling	X	.	.	.	.	.	X
	Ploughing	X	.	.	.	.	.	X
4514	Salivation, Moderate	.	X	.	.	.	.	X
	Salivation, Severe	X	.	.	.	.	X	.
	Salivation, Slight	.	.	X	X	.	.	.
	Pedaling	X	.	.	.	.	.	X
	Ploughing	X	.	.	.	.	X	X
4515	Salivation, Moderate	.	.	.	.	.	.	X
	Salivation, Slight	.	.	.	.	.	X	.
	Pedaling	.	.	.	.	.	.	X
	Ploughing	X	.	.	.	.	X	X

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 7

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

0 mg/kg /day Group 1	Day(s) Relative to Start Date						
	-7	1	8	16	22	29	36
1001	148	198	245 [a]	287	325	350	371
1002	133	183	227 [b]	272	306	330	359
1003	136	174	207	245	268	287	308
1004	144	198	246 [c]	294	328	348	374
1005	141	182	221 [d]	259	286	312	338
1006	156	196	231	278 [x]	306	337	358
1007	137	180	222 [e]	260	287	307	325
1008	142	188	226	260	291	312	337
1009	155	206	256 [x]	298	325	351	374
1010	140	189	236 [x]	275	312	337	365
1011	153	203	250 [x]	290	323	351	375
1012	145	189	228 [x]	262	291	316	336
1013	124	175	219 [x]	260	290	317	341
1014	159	210	255 [x]	291	321	349	369
1015	129	178	223 [x]	267	297	313	331
Mean	142.8	189.9	232.8	273.2	303.7	327.8	350.7
SD	10.2	11.4	14.6	15.9	18.3	20.1	21.2
N	15	15	15	15	15	15	15

[x] = See Comments and Markers page

[a] [RC:245g weight verified]

[b] [RC:227g weight verified]

[c] [RC:246g weight verified]

[d] [RC:221g weight verified]

[e] [RC:222g weight verified]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 7

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

0 mg/kg /day Group 1	Day(s) Relative to Start Date						
	43	50	57	64	71	78	84
1001	387	399	412	421	431	445	450
1002	378	398	416	432	442	448	463
1003	322	330	349	354	368	376	384
1004	395	413	422	436	450	465	473
1005	354	360	371	381	396	410	410
1006	380	384	400	405	413	425	434
1007	343	358	370	383	390	395	409
1008	354	372	380	399	408	415	426
1009	389	404	419	425	436	450	460
1010	380	396	414	421	434	439	449
1011	390	406	416	426	438	447	452
1012	351	371	383	391	402	410	418
1013	360	376	390	402	417	425	432
1014	380	396	410	416	427	433	442
1015	338	355	360	369	379	383	396
Mean	366.7	381.2	394.1	404.1	415.4	424.4	433.2
SD	22.2	23.5	23.9	24.4	24.5	26.1	25.9
N	15	15	15	15	15	15	15

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

0 mg/kg /day Group 1	Day(s) Relative to Start Date				
	90	98	105	112	119
1001	453	-	-	-	-
1002	472	-	-	-	-
1003	390	-	-	-	-
1004	485	-	-	-	-
1005	418	-	-	-	-
1006	444	-	-	-	-
1007	415	-	-	-	-
1008	427	-	-	-	-
1009	463	-	-	-	-
1010	455	-	-	-	-
1011	451	459	463	466	473
1012	428	432	432	436	446
1013	441	446	444	435	454
1014	451	456	457	464	471
1015	401	409	411	416	415
Mean	439.6	440.4	441.4	443.4	451.8
SD	26.3	20.5	20.8	21.3	23.5
N	15	5	5	5	5

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 7

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

500 mg/kg /day Group 2	Day(s) Relative to Start Date						
	-7	1	8	16	22	29	36
2001	145	191	239 [a]	270	294	311	329
2002	145	188	232 [b]	268	299	315	342
2003	134	180	227 [c]	270	297	327	351
2004	125	169	212 [d]	256 [x]	283	309	335
2005	115	161	202 [e]	256 [x]	283	313	338
2006	129	178	223 [x]	268	298	327	355
2007	141	186	222	255	272	290	303
2008	140	184	224 [x]	269 [x]	296	320	339
2009	145	191	235 [x]	281	302	325	337
2010	125	169	212 [d]	256 [x]	279	301	317
Mean	134.4	179.7	222.8	264.9	290.3	313.8	334.6
SD	10.5	10.3	11.5	8.7	10.2	11.9	15.3
N	10	10	10	10	10	10	10
%Diff	-5.9	-5.4	-4.3	-3.0	-4.4	-4.3	-4.6

[x] = See Comments and Markers page

[a] [RC:239g weight verified]

[b] [RC:232g weight verified]

[c] [RC:227g weight verified]

[d] [RC:212g weight verified]

[e] [RC:202g weight verified]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

500 mg/kg /day Group 2	Day(s) Relative to Start Date						
	43	50	57	64	71	78	84
2001	336	357	363	381	382	392	403
2002	359	372	385	399	403	401	414
2003	369	391	405	420	433	439	446
2004	355	372	379	402	409	422	424
2005	364	377	393	413	429	434	447
2006	375	388	402	416	427	434	448
2007	312	333	337	352	364	375	388
2008	358	373	384	399	407	414	417
2009	361	372	376	391	398	399	407
2010	336	352	359	372	381	385	391
Mean	352.5	368.7	378.3	394.5	403.3	409.5	418.5
SD	19.0	17.3	20.8	21.2	22.8	22.4	22.5
N	10	10	10	10	10	10	10
%Diff	-3.9	-3.3	-4.0	-2.4	-2.9	-3.5	-3.4

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

500 mg/kg /day Group 2	Day(s) Relative to Start Date
	90
2001	407
2002	417
2003	453
2004	432
2005	456
2006	455
2007	390
2008	423
2009	416
2010	400
Mean	424.9
SD	23.6
N	10
%Diff	-3.3

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

1000 mg/kg /day Group 3	Day(s) Relative to Start Date						
	-7	1	8	16	22	29	36
3001	114	167	213 [a]	258 [x]	283	303	320
3002	123	176	217 [b]	262 [x]	291	319	343
3003	137	186	230 [c]	277 [x]	303	315	328
3004	139	191	239 [d]	285	312	337	355
3005	120	166	209 [e]	247	274	289	301
3006	148	198	245 [x]	294	324	351	368
3007	161	206	238	268	274	283	292
3008	142	186	225 [x]	263	285	290	304
3009	144	184	226 [x]	269	288	301	319
3010	135	180	218 [x]	262	287	303	320
Mean	136.3	184.0	226.0	268.5	292.1	309.1	325.0
SD	14.1	12.6	12.0	13.7	16.2	21.7	24.2
N	10	10	10	10	10	10	10
%Diff	-4.6	-3.1	-2.9	-1.7	-3.8	-5.7	-7.3

[x] = See Comments and Markers page

[a] [RC:213g weight verified]

[b] [RC:217g weight verified]

[c] [RC:230g weight verified]

[d] [RC:239g weight verified]

[e] [RC:209g weight verified]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

1000 mg/kg /day Group 3	Day(s) Relative to Start Date						
	43	50	57	64	71	78	84
3001	340	357	368	389	401	413	428
3002	364	373	393	402	414	420	428
3003	329	341	356	363	371	375	387
3004	369	382	394	407	416	418	423
3005	315	322	328	342	352	354	365
3006	391	405	422	436	448	453	461
3007	308	328	336	352	357	363	371
3008	309	320	333	342	348	349	359
3009	334	346	358	373	379	390	392
3010	335	346	354	365	373	377	384
Mean	339.4	352.0	364.2	377.1	385.9	391.2	399.8
SD	27.5	27.6	30.5	30.9	32.7	33.8	33.4
N	10	10	10	10	10	10	10
%Diff	-7.5	-7.7	-7.6	-6.7	-7.1	-7.8	-7.7

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

1000 mg/kg /day Group 3	Day(s) Relative to Start Date
	90
3001	430
3002	427
3003	395
3004	430
3005	367
3006	472
3007	375
3008	365
3009	402
3010	392
Mean	405.5
SD	34.1
N	10
%Diff	-7.8

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

2000 mg/kg /day Group 4	Day(s) Relative to Start Date						
	-7	1	8	16	22	29	36
4001	151	204	245	294	331	358	383
4002	125	176	220 [a]	274 [x]	312	341	368
4003	144	198	240 [b]	273	303	315	335
4004	122	174	217 [c]	264 [x]	297	316	334
4005	128	175	207	254 [x]	279	303	326
4006	134	184	223 [d]	251	272	285	295
4007	131	178	221 [e]	265 [x]	291	320	330
4008	124	172	215 [x]	260 [x]	291	320	346
4009	130	181	214	255	274	285	301
4010	128	173	210 [x]	256 [x]	275	298	310
4011	144	190	237 [x]	283	294	318	326
4012	130	181	218 [x]	263 [x]	284	314	334
4013	164	222	263	309	339	358	368
4014	148	198	239 [x]	271	302	330	344
4015	132	179	215	223	266	294	304
Mean	135.7	185.7	225.6	266.3	294.0	317.0	333.6
SD	11.9	14.2	15.7	19.9	21.1	22.8	25.6
N	15	15	15	15	15	15	15
%Diff	-5.0	-2.2	-3.1	-2.5	-3.2	-3.3	-4.9

[x] = See Comments and Markers page

[a] [RC:220g weight verified]

[b] [RC:240g weight verified]

[c] [RC:217g weight verified]

[d] [RC:223g weight verified]

[e] [RC:221g weight verified]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

2000 mg/kg /day Group 4	Day(s) Relative to Start Date						
	43	50	57	64	71	78	84
4001	400	419	427	441	455	466	480
4002	389	414	431	458	465	476	484
4003	351	361	375	392	399	401	414
4004	346	362	376	396	396	402	410
4005	334	344	361	374	379	385	393
4006	306	318	332	343	355	360	371
4007	351	365	373	391	403	407	413
4008	362	377	383	400	410	415	416
4009	316	335	351	361	367	376	381
4010	323	336	343	359	371	375	381
4011	338	349	361	376	393	399	409
4012	358	362	375	384	395	397	410
4013	373	395	411	428	439	445	447
4014	364	381	385	402	404	409	420
4015	331	341	344	356	364	369	381
Mean	349.5	363.9	375.2	390.7	399.7	405.5	414.0
SD	26.1	29.1	29.4	32.3	32.4	33.9	33.8
N	15	15	15	15	15	15	15
%Diff	-4.7	-4.5	-4.8	-3.3	-3.8	-4.5	-4.4

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Male Bodyweight (g)

2000 mg/kg /day Group 4	Day(s) Relative to Start Date				
	90	98	105	112	119
4001	483	-	-	-	-
4002	480	-	-	-	-
4003	418	-	-	-	-
4004	414	-	-	-	-
4005	399	-	-	-	-
4006	375	-	-	-	-
4007	420	-	-	-	-
4008	430	-	-	-	-
4009	388	-	-	-	-
4010	385	-	-	-	-
4011	415	415	421	424	432
4012	411	408	402	407	406
4013	454	455	453	458	464
4014	419	427	427	431	435
4015	381	390	391	390	392
Mean	418.1	419.0	418.8	422.0	425.8
SD	32.9	24.2	24.0	25.6	27.9
N	15	5	5	5	5
%Diff	-4.9	-4.9	-5.1	-4.8	-5.8

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

0 mg/kg /day Group 1	Day(s) Relative to Start Date						
	-7	1	8	16	22	29	36
1501	121	144	166	183	195	197	216
1502	132	159	175	196	197	215	230
1503	126	150	166	184	197	208	221
1504	146	169	193	209	226	230	250
1505	120	153	171	200	200	215	235
1506	119	152	169	184	194	211	225
1507	125	152	171	188	196	203	225
1508	123	146	149	178	198	215	210
1509	121	135	143	160	169	179	180
1510	131	153	160	184	187	208	217
1511	127	163	162	185	201	213	213
1512	126	149	176	198	210	216	231
1513	125	156	181	207	215	242	253
1514	122	145	157	182	200	206	207
1515	147	176	193	216	219	240	262
Mean	127.4	153.5	168.8	190.3	200.3	213.2	225.0
SD	8.6	10.3	14.0	14.2	13.6	15.8	20.4
N	15	15	15	15	15	15	15

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

0 mg/kg /day Group 1	Day(s) Relative to Start Date						
	43	50	57	64	71	78	84
1501	222	227	228	236	241	245	249
1502	234	238	248	258	256	259	267
1503	221	238	242	247	243	250	256
1504	256	263	258	274	307	287 [a]	299
1505	245	249	258	269	270	270	290
1506	224	222	239	245	250	243	252
1507	232	240	239	253	260	263	264
1508	231	238	241	238	249	252	249
1509	181	194	202	201	201	207	209
1510	221	220	231	237	239	237	247
1511	231	243	240	235	247	252	249
1512	242	244	241	254	259	262	264
1513	263	267	277	288	286	289	299
1514	225	235	238	236	244	250	249
1515	261	262	270	277	280	281	293
Mean	232.6	238.7	243.5	249.9	255.5	256.5	262.4
SD	20.2	18.6	17.9	21.7	24.4	20.9	24.4
N	15	15	15	15	15	15	15

[a] [RC:287g weight verified]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

0 mg/kg /day Group 1	Day(s) Relative to Start Date				
	90	98	105	112	119
1501	249	-	-	-	-
1502	263	-	-	-	-
1503	258	-	-	-	-
1504	297	-	-	-	-
1505	276 [a]	-	-	-	-
1506	247	-	-	-	-
1507	262	-	-	-	-
1508	265	-	-	-	-
1509	210	-	-	-	-
1510	239	-	-	-	-
1511	259	269	263	259	263
1512	265	267	265	270	271
1513	324	300 [b]	301	308	307
1514	257	259	258	255	263
1515	288	292	296	300	292
Mean	263.9	277.4	276.6	278.4	279.2
SD	26.2	17.6	20.2	24.2	19.5
N	15	5	5	5	5

[a] [RC:276g weight verified]

[b] [RC:300g weight verified]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

500 mg/kg /day Group 2	Day(s) Relative to Start Date						
	-7	1	8	16	22	29	36
2501	132	143	170	188	202	211	222
2502	123	146	160	183	195	205	204
2503	133	159	174	207	225	239	247
2504	127	158	175	198	221	232	239
2505	121	149	169	191	198	217	232
2506	127	154	182	208	220	225	244
2507	120	143	167	190	197	200	220
2508	136	157	164	185	204	214	218
2509	116	144	163	188	202	216	230
2510	135	150	167	189	201	208	216
Mean	127.0	150.3	169.1	192.7	206.5	216.7	227.2
SD	6.9	6.3	6.5	8.7	11.1	12.2	13.6
N	10	10	10	10	10	10	10
%Diff	-0.3	-2.1	0.2	1.3	3.1	1.6	1.0

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

500 mg/kg /day Group 2	Day(s) Relative to Start Date						
	43	50	57	64	71	78	84
2501	230	233	230	240	246	243	249
2502	222	229	228	227	239	248	245
2503	256	272	270	273	285	287	287
2504	241	257	262	264	262	273	273
2505	233	232	247	254	257	252	263
2506	258	261	258	274	258 [a]	278	289
2507	231	234	234	247	252	246	257
2508	232	244	245	246	258	266	265
2509	233	249	255	260	258	266	277
2510	228	236	237	240	246	246	248
Mean	236.4	244.7	246.6	252.5	256.1	260.5	265.3
SD	11.8	14.6	14.4	15.3	12.4	15.6	15.9
N	10	10	10	10	10	10	10
%Diff	1.6	2.5	1.3	1.1	0.2	1.6	1.1

[a] [RC:258g weight verified]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

500 mg/kg /day Group 2	Day(s) Relative to Start Date
	90
2501	251
2502	249
2503	291
2504	274
2505	255
2506	292
2507	257
2508	266
2509	274
2510	254
Mean	266.3
SD	15.9
N	10
%Diff	0.9

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

1000 mg/kg /day Group 3	Day(s) Relative to Start Date						
	-7	1	8	16	22	29	36
3501	139	167	184	209	220	238	241
3502	135	155	169	192	198	203	221
3503	117	137	163	185	199	207	225
3504	142	160	193 [a]	212	227	234	263
3505	136	156	170	200	219	232	232
3506	137	165	184	200	208	222	233
3507	137	168	189	215	219	242	256
3508	119	151	175	201	204	219	235
3509	126	149	166	189	204	214	221
3510	125	149	177	204	218	231	246
Mean	131.3	155.7	177.0	200.7	211.6	224.2	237.3
SD	8.8	9.7	10.2	9.8	10.2	13.3	14.3
N	10	10	10	10	10	10	10
%Diff	3.1	1.5	4.9	5.5	5.7	5.2	5.5

[a] [RC:193g weight verified]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

1000 mg/kg /day Group 3	Day(s) Relative to Start Date						
	43	50	57	64	71	78	84
3501	245	261	265	270	266	279	277
3502	226	232	232	245	248	248	251
3503	241	241	237	258	264	263	265
3504	271	275	270	281	289	292	297
3505	249	259	262	265	273	275	267
3506	242	273	250 [a]	262	262	259	272
3507	262	262	281	292	294	289	299
3508	242	241	256	265	267	262	272
3509	222	239	249	252	243	253	261
3510	263	269	266	280	291	292	297
Mean	246.3	255.2	256.8	267.0	269.7	271.2	275.8
SD	15.7	15.6	15.1	14.2	17.4	16.4	16.7
N	10	10	10	10	10	10	10
%Diff	5.9	6.9	5.5	6.9	5.6	5.7	5.1

[a] [RC:251g weight verified]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

1000 mg/kg /day Group 3	Day(s) Relative to Start Date
	90
3501	274
3502	253
3503	269
3504	299
3505	277
3506	267
3507	297
3508	267
3509	258
3510	303
Mean	276.4
SD	17.5
N	10
%Diff	4.7

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

2000 mg/kg /day Group 4	Day(s) Relative to Start Date						
	-7	1	8	16	22	29	36
4501	132	156	166	190	205	220	221
4502	134	162	183	198	211	216	231
4503	122	138	162	183	196	200	213
4504	122	143	162	180	187	206	214
4505	133	155	184	202	221	227	245
4506	131	151	175	193	203	212	225
4507	140	168	187	217	236	253	257
4508	140	172	199	225	237	255	264
4509	130	150	166	194	214	226	224
4510	131	165	189	212	217	242	251
4511	137	158	191 [a]	214	227	238	250
4512	127	151	177	203	211	222	236
4513	112	134	150	171	191	208	204
4514	130	160	183	212	215	246	258
4515	125	156	173	195	213	225	230
Mean	129.7	154.6	176.5	199.3	212.3	226.4	234.9
SD	7.4	10.6	13.3	15.0	14.6	17.1	18.5
N	15	15	15	15	15	15	15
%Diff	1.8	0.7	4.5	4.7	6.0	6.2	4.4

[a] [RC:191g weight verified]

Sponsor Reference No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

2000 mg/kg /day Group 4	Day(s) Relative to Start Date						
	43	50	57	64	71	78	84
4501	241	253	256	256	261	264	262
4502	242	247	242	254	257	254	262
4503	221	227	226	232	242	245	245
4504	224	228	238	246	253	249	255
4505	254	263	268	278	285	289	294
4506	235	239	238	249	254	250	254
4507	272	277	281	280	288	289	286
4508	273	287	295	305	306	311	319
4509	242	249	251	258	264	268	265
4510	261	257	267	274	274	270	283
4511	265	265	260	272	281	279	278
4512	248	249	246	264	269	264	271
4513	224	233	243	238	257	261	250
4514	260	266	272	280	284	279	290
4515	244	250	251	250	260	263	261
Mean	247.1	252.7	255.6	262.4	269.0	269.0	271.7
SD	16.9	17.2	18.4	19.2	17.0	17.9	19.9
N	15	15	15	15	15	15	15
%Diff	6.2	5.9	5.0	5.0	5.3	4.9	3.5

Sponsor Reference No. (b) (4)

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Individual Body Weights

(b) (4)

Sex: Female Bodyweight (g)

2000 mg/kg /day Group 4	Day(s) Relative to Start Date				
	90	98	105	112	119
4501	271	-	-	-	-
4502	258	-	-	-	-
4503	247	-	-	-	-
4504	253	-	-	-	-
4505	288	-	-	-	-
4506	260	-	-	-	-
4507	294	-	-	-	-
4508	321	-	-	-	-
4509	270	-	-	-	-
4510	279	-	-	-	-
4511	283	276 [a]	274	271	271
4512	272	273	266	273	276
4513	266	268	259	258	267
4514	284	278 [b]	288	289	288
4515	262	260	260	256	256
Mean	273.9	271.0	269.4	269.4	271.6
SD	18.7	7.2	12.0	13.3	11.8
N	15	5	5	5	5
%Diff	3.8	-2.3	-2.6	-3.2	-2.7

[a] [RC:276g weight verified]

[b] [RC:278g weight verified]

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Individual Body Weights

(b) (4)

Comments and Markers

Page	Measurement		Group	Sex	Subject	Day	Type	Marker
	Bodyweight		1	Male	1001	8	Result	
		Comment: 245g weight verified						
	Bodyweight		1	Male	1002	8	Result	
		Comment: 227g weight verified						
	Bodyweight		1	Male	1004	8	Result	
		Comment: 246g weight verified						
	Bodyweight		1	Male	1005	8	Result	
		Comment: 221g weight verified						
	Bodyweight		1	Male	1006	16	Result	
		Comment: 278g weight verified						
	Bodyweight		1	Male	1007	8	Result	
		Comment: 222g weight verified						
	Bodyweight		1	Male	1009	8	Result	
		Comment: 256g weight verified						
	Bodyweight		1	Male	1010	8	Result	
		Comment: 236g weight verified						
	Bodyweight		1	Male	1011	8	Result	
		Comment: 250g weight verified						
	Bodyweight		1	Male	1012	8	Result	
		Comment: 228g weight verified						
	Bodyweight		1	Male	1013	8	Result	
		Comment: 219g weight verified						
	Bodyweight		1	Male	1014	8	Result	
		Comment: 255g weight verified						
	Bodyweight		1	Male	1015	8	Result	
		Comment: 223g weight verified						
	Bodyweight		2	Male	2001	8	Result	
		Comment: 239g weight verified						

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Individual Body Weights

(b) (4)

Comments and Markers

Page	Measurement		Group	Sex	Subject	Day	Type	Marker
	Bodyweight		2	Male	2002	8	Result	
		Comment: 232g weight verified						
	Bodyweight		2	Male	2003	8	Result	
		Comment: 227g weight verified						
	Bodyweight		2	Male	2004	8	Result	
		Comment: 212g weight verified						
	Bodyweight		2	Male	2004	16	Result	
		Comment: 257g weight verified						
	Bodyweight		2	Male	2005	8	Result	
		Comment: 202g weight verified						
	Bodyweight		2	Male	2005	16	Result	
		Comment: 257g weight verified						
	Bodyweight		2	Male	2006	8	Result	
		Comment: 223g weight verified						
	Bodyweight		2	Male	2008	8	Result	
		Comment: 224g weight verified						
	Bodyweight		2	Male	2008	16	Result	
		Comment: 269g weight verified						
	Bodyweight		2	Male	2009	8	Result	
		Comment: 235g weight verified						
	Bodyweight		2	Male	2010	8	Result	
		Comment: 212g weight verified						
	Bodyweight		2	Male	2010	16	Result	
		Comment: 256g weight verified						
	Bodyweight		3	Male	3001	8	Result	
		Comment: 213g weight verified						
	Bodyweight		3	Male	3001	16	Result	
		Comment: 257g weight verified						

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Individual Body Weights

(b) (4)

Comments and Markers

Page	Measurement		Group	Sex	Subject	Day	Type	Marker
	Bodyweight		3	Male	3002	8	Result	
		Comment: 217g weight verified						
	Bodyweight		3	Male	3002	16	Result	
		Comment: 262g weight verified						
	Bodyweight		3	Male	3003	8	Result	
		Comment: 230g weight verified						
	Bodyweight		3	Male	3003	16	Result	
		Comment: 277g weight verified						
	Bodyweight		3	Male	3004	8	Result	
		Comment: 239g weight verified						
	Bodyweight		3	Male	3005	8	Result	
		Comment: 209g weight verified						
	Bodyweight		3	Male	3006	8	Result	
		Comment: 245g weight verified						
	Bodyweight		3	Male	3008	8	Result	
		Comment: 225g weight verified						
	Bodyweight		3	Male	3009	8	Result	
		Comment: 226g weight verified						
	Bodyweight		3	Male	3010	8	Result	
		Comment: 218g weight verified						
	Bodyweight		4	Male	4002	8	Result	
		Comment: 220g weight verified						
	Bodyweight		4	Male	4002	16	Result	
		Comment: 275g weight verified						
	Bodyweight		4	Male	4003	8	Result	
		Comment: 240g weight verified						
	Bodyweight		4	Male	4004	8	Result	
		Comment: 217g weight verified						

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Individual Body Weights

(b) (4)

Comments and Markers

Page	Measurement		Group	Sex	Subject	Day	Type	Marker
	Bodyweight		4	Male	4004	16	Result	
		Comment: 264g weight verified						
	Bodyweight		4	Male	4005	16	Result	
		Comment: 254g weight verified						
	Bodyweight		4	Male	4006	8	Result	
		Comment: 223g weight verified						
	Bodyweight		4	Male	4007	8	Result	
		Comment: 221g weight verified						
	Bodyweight		4	Male	4007	16	Result	
		Comment: 265g weight verified						
	Bodyweight		4	Male	4008	8	Result	
		Comment: 215g weight verified						
	Bodyweight		4	Male	4008	16	Result	
		Comment: 259g weight verified						
	Bodyweight		4	Male	4010	8	Result	
		Comment: 210g weight verified						
	Bodyweight		4	Male	4010	16	Result	
		Comment: 256g weight verified						
	Bodyweight		4	Male	4011	8	Result	
		Comment: 237g weight verified						
	Bodyweight		4	Male	4012	8	Result	
		Comment: 218g weight verified						
	Bodyweight		4	Male	4012	16	Result	
		Comment: 263g weight verified						
	Bodyweight		4	Male	4014	8	Result	
		Comment: 239g weight verified						
	Bodyweight		1	Female	1504	78	Result	
		Comment: 287g weight verified						

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Individual Body Weights

(b) (4)

Comments and Markers

Page	Measurement		Group	Sex	Subject	Day	Type	Marker
	Bodyweight		1	Female	1505	90	Result	
		Comment: 276g weight verified						
	Bodyweight		1	Female	1513	98	Result	
		Comment: 300g weight verified						
	Bodyweight		2	Female	2506	71	Result	
		Comment: 258g weight verified						
	Bodyweight		3	Female	3504	8	Result	
		Comment: 193g weight verified						
	Bodyweight		3	Female	3506	57	Result	
		Comment: 251g weight verified						
	Bodyweight		4	Female	4511	8	Result	
		Comment: 191g weight verified						
	Bodyweight		4	Female	4511	98	Result	
		Comment: 276g weight verified						
	Bodyweight		4	Female	4514	98	Result	
		Comment: 278g weight verified						

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Appendix 8

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Individual Food Consumption

(b) (4)

Sex: Male Daily Food Cons Per Animal (g)

0 mg/kg /day Group 1	No. in Cage	Day(s) Relative to Animal Start Date						
		1 → 8	8 → 16	16 → 22	22 → 29	29 → 36	36 → 43	43 → 50
1	3	23	26	28	27	27	27	27
2	3	23	27	28	28	28	28	28
3	4	23	25	26	26	26	26	24
4	3	23	26	28	27	27	26	25
5	2	24	26	28	27	27	25	25
	Mean	23.1	25.9	27.4	26.9	27.1	26.4	25.8
	SD	0.4	0.5	0.9	1.0	0.8	1.1	1.4
	N	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Food Consumption

(b) (4)

Sex: Male Daily Food Cons Per Animal (g)

0 mg/kg /day Group 1	No. in Cage	Day(s) Relative to Animal Start Date						
		50 → 57	57 → 64	64 → 71	71 → 78	78 → 84	84 → 90	90 → 98
1	3	21	26	25	26	25	25	-
2	3	27	26	25	26	25	25	-
3	4	23	24	23	23	23	22	-
4	3	29	24	24	24	25	23	24
5	2	22	25	24	25	25	23	26
	Mean	24.4	24.8	24.4	24.9	24.6	23.5	25.0
	SD	3.3	1.0	0.9	1.1	1.1	1.3	0.9
	N	5	5	5	5	5	5	2

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Food Consumption

(b) (4)

Sex: Male Daily Food Cons Per Animal (g)

0 mg/kg /day Group 1	No. in Cage	Day(s) Relative to Animal Start Date		
		98 → 105	105 → 112	112 → 119
1	3	-	-	-
2	3	-	-	-
3	4	-	-	-
4	3	24	24	25
5	2	25	26	25
Mean		24.3	25.0	24.8
SD		1.0	0.8	0.1
N		2	2	2

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Food Consumption

(b) (4)

Sex: Male Daily Food Cons Per Animal (g)

500 mg/kg /day Group 2	No. in Cage	Day(s) Relative to Animal Start Date						
		1 → 8	8 → 16	16 → 22	22 → 29	29 → 36	36 → 43	43 → 50
9	3	23	26	27	25	27	26	26
10	3	23	27	28	27	29	28	22
11	4	23	26	26	25	25	25	25
	Mean	23.0	26.1	26.9	25.8	26.8	26.1	24.2
	SD	0.5	0.5	0.7	1.3	1.7	1.5	2.3
	N	3	3	3	3	3	3	3
	%Diff	-0.5	0.8	-1.7	-4.3	-1.1	-1.2	-6.3

Sponsor Reference No. (b) (4)

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Individual Food Consumption

(b) (4)

Sex: Male Daily Food Cons Per Animal (g)

500 mg/kg /day Group 2	No. in Cage	Day(s) Relative to Animal Start Date					
		50 → 57	57 → 64	64 → 71	71 → 78	78 → 84	84 → 90
9	3	24	25	25	24	24	23
10	3	25	26	26	26	26	25
11	4	23	23	23	23	23	22
	Mean	24.0	24.7	24.5	24.6	24.3	23.3
	SD	1.3	1.3	1.5	1.6	1.7	1.7
	N	3	3	3	3	3	3
	%Diff	-1.5	-0.3	0.1	-1.3	-1.6	-0.9

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Food Consumption

(b) (4)

Sex: Male Daily Food Cons Per Animal (g)

1000 mg/kg /day Group 3	No. in Cage	Day(s) Relative to Animal Start Date						
		1 → 8	8 → 16	16 → 22	22 → 29	29 → 36	36 → 43	43 → 50
14	3	23	26	26	24	24	24	26
15	3	24	27	27	26	26	26	24
16	4	22	25	23	22	22	22	19
Mean		23.0	26.1	25.5	24.0	23.8	23.9	23.0
SD		1.3	1.1	2.0	2.1	1.9	1.8	4.0
N		3	3	3	3	3	3	3
%Diff		-0.7	0.7	-6.8	-10.8	-12.1	-9.6	-11.1

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Food Consumption

(b) (4)

Sex: Male Daily Food Cons Per Animal (g)

1000 mg/kg /day Group 3	No. in Cage	Day(s) Relative to Animal Start Date					
		50 → 57	57 → 64	64 → 71	71 → 78	78 → 84	84 → 90
14	3	23	23	23	23	23	22
15	3	24	24	23	24	23	22
16	4	21	23	22	22	22	21
Mean		22.9	23.1	22.5	23.0	22.4	21.9
SD		1.5	0.5	0.8	1.0	0.7	0.7
N		3	3	3	3	3	3
%Diff		-6.2	-6.5	-7.8	-7.8	-9.1	-7.0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Food Consumption

(b) (4)

Sex: Male Daily Food Cons Per Animal (g)

2000 mg/kg /day Group 4	No. in Cage	Day(s) Relative to Animal Start Date						
		1 → 8	8 → 16	16 → 22	22 → 29	29 → 36	36 → 43	43 → 50
19	3	25	30	32	32	31	31	30
20	3	22	25	25	24	24	23	23
21	4	23	26	27	26	26	25	25
22	3	23	27	28	27	27	26	26
23	2	24	25	25	27	26	26	20
	Mean	23.4	26.8	27.4	27.0	26.7	26.1	25.0
	SD	1.3	2.1	2.9	2.9	2.6	2.7	3.8
	N	5	5	5	5	5	5	5
	%Diff	1.1	3.4	-0.1	0.3	-1.4	-1.1	-3.2

Sponsor Reference No. (b) (4)

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Individual Food Consumption

(b) (4)

Sex: Male Daily Food Cons Per Animal (g)

2000 mg/kg /day Group 4	No. in Cage	Day(s) Relative to Animal Start Date						
		50 → 57	57 → 64	64 → 71	71 → 78	78 → 84	84 → 90	90 → 98
19	3	29	30	29	29	29	26	-
20	3	22	23	22	22	22	21	-
21	4	24	24	24	24	23	22	-
22	3	24	25	25	26	25	24	25
23	2	23	24	23	24	25	22	25
	Mean	24.4	25.1	24.6	24.9	24.8	23.1	24.6
	SD	2.6	2.7	2.7	2.4	2.6	2.1	0.2
	N	5	5	5	5	5	5	2
	%Diff	0.3	1.5	0.7	-0.2	0.8	-2.0	-1.5

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Individual Food Consumption

(b) (4)

Sex: Male Daily Food Cons Per Animal (g)

2000 mg/kg /day Group 4	No. in Cage	Day(s) Relative to Animal Start Date		
		98 → 105	105 → 112	112 → 119
19	3	-	-	-
20	3	-	-	-
21	4	-	-	-
22	3	24	25	25
23	2	24	24	24
Mean		23.9	24.0	24.7
SD		0.1	0.8	1.0
N		2	2	2
%Diff		-1.5	-3.7	-0.1

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Individual Food Consumption

(b) (4)

Sex: Female Daily Food Cons Per Animal (g)

0 mg/kg /day Group 1	No. in Cage	Day(s) Relative to Animal Start Date						
		1 → 8	8 → 16	16 → 22	22 → 29	29 → 36	36 → 43	43 → 50
6	5	17	19	19	19	20	20	20
7	5	15	17	17	17	18	18	18
8	5	17	19	19	19	20	20	19
	Mean	16.4	18.2	18.5	18.5	19.6	19.2	18.9
	SD	1.3	1.0	0.9	0.9	1.0	0.7	1.0
	N	3	3	3	3	3	3	3

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Individual Food Consumption

(b) (4)

Sex: Female Daily Food Cons Per Animal (g)

0 mg/kg /day Group 1	No. in Cage	Day(s) Relative to Animal Start Date						
		50 → 57	57 → 64	64 → 71	71 → 78	78 → 84	84 → 90	90 → 98
6	5	18	19	18	19	19	17	-
7	5	18	18	17	18	18	17	-
8	5	19	19	18	19	19	17	18
	Mean	18.2	18.5	17.9	18.4	18.9	16.8	18.3
	SD	0.5	0.6	0.5	0.5	0.7	0.3	-
	N	3	3	3	3	3	3	1

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Individual Food Consumption

(b) (4)

Sex: Female Daily Food Cons Per Animal (g)

0 mg/kg /day Group 1	No. in Cage	Day(s) Relative to Animal Start Date		
		98 → 105	105 → 112	112 → 119
6	5	-	-	-
7	5	-	-	-
8	5	18	18	18
	Mean	18.3	18.3	17.7
	SD	-	-	-
	N	1	1	1

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Individual Food Consumption

(b) (4)

Sex: Female Daily Food Cons Per Animal (g)

500 mg/kg /day Group 2	No. in Cage	Day(s) Relative to Animal Start Date						
		1 → 8	8 → 16	16 → 22	22 → 29	29 → 36	36 → 43	43 → 50
12	5	17	19	20	19	20	20	20
13	5	17	22	19	18	20	20	23
	Mean	16.8	20.4	19.5	18.5	19.8	19.8	21.4
	SD	0.3	1.6	0.4	0.8	0.1	0.3	2.3
	N	2	2	2	2	2	2	2
	%Diff	2.0	12.1	5.4	0.4	1.4	3.1	13.2

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Individual Food Consumption

(b) (4)

Sex: Female Daily Food Cons Per Animal (g)

500 mg/kg /day Group 2	No. in Cage	Day(s) Relative to Animal Start Date					
		50 → 57	57 → 64	64 → 71	71 → 78	78 → 84	84 → 90
12	5	17	18	18	18	18	17
13	5	18	19	18	19	19	17
	Mean	17.7	18.6	18.4	18.7	18.7	16.9
	SD	0.6	0.8	0.1	0.2	1.0	0.4
	N	2	2	2	2	2	2
	%Diff	-2.9	0.9	3.0	1.7	-1.3	0.7

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Individual Food Consumption

(b) (4)

Sex: Female Daily Food Cons Per Animal (g)

1000 mg/kg /day Group 3	No. in Cage	Day(s) Relative to Animal Start Date						
		1 → 8	8 → 16	16 → 22	22 → 29	29 → 36	36 → 43	43 → 50
17	5	16	20	21	19	21	21	20
18	5	18	20	20	20	21	21	21
	Mean	16.9	20.2	20.5	19.6	20.8	20.8	20.5
	SD	1.7	0.0	0.3	0.3	0.0	0.0	0.0
	N	2	2	2	2	2	2	2
	%Diff	2.6	11.5	10.5	6.2	6.3	8.1	8.5

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Individual Food Consumption

(b) (4)

Sex: Female Daily Food Cons Per Animal (g)

1000 mg/kg /day Group 3	No. in Cage	Day(s) Relative to Animal Start Date					
		50 → 57	57 → 64	64 → 71	71 → 78	78 → 84	84 → 90
17	5	19	20	19	20	20	18
18	5	19	20	19	19	20	18
	Mean	19.0	20.0	19.2	19.5	20.0	17.8
	SD	0.3	0.1	0.2	0.1	0.0	0.2
	N	2	2	2	2	2	2
	%Diff	4.1	8.0	7.3	6.5	5.7	5.9

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Individual Food Consumption

(b) (4)

Sex: Female Daily Food Cons Per Animal (g)

2000 mg/kg /day Group 4	No. in Cage	Day(s) Relative to Animal Start Date						
		1 → 8	8 → 16	16 → 22	22 → 29	29 → 36	36 → 43	43 → 50
24	5	16	21	19	18	20	20	19
25	5	18	21	22	20	21	21	21
26	5	17	20	21	21	21	21	22
	Mean	17.1	20.5	20.5	19.8	20.6	20.7	20.5
	SD	0.9	0.5	1.1	1.2	0.8	0.6	1.1
	N	3	3	3	3	3	3	3
	%Diff	4.3	12.7	10.5	7.1	5.5	7.8	8.7

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Individual Food Consumption

(b) (4)

Sex: Female Daily Food Cons Per Animal (g)

2000 mg/kg /day Group 4	No. in Cage	Day(s) Relative to Animal Start Date						
		50 → 57	57 → 64	64 → 71	71 → 78	78 → 84	84 → 90	90 → 98
24	5	18	19	19	19	19	17	-
25	5	20	21	20	20	20	19	-
26	5	20	21	20	20	20	18	19
	Mean	19.3	20.4	19.6	19.5	19.9	17.9	19.5
	SD	0.9	0.8	0.9	0.6	0.5	1.2	-
	N	3	3	3	3	3	3	1
	%Diff	5.7	10.2	9.5	6.3	5.1	6.7	6.4

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Individual Food Consumption

(b) (4)

Sex: Female Daily Food Cons Per Animal (g)

2000 mg/kg /day Group 4	No. in Cage	Day(s) Relative to Animal Start Date		
		98 → 105	105 → 112	112 → 119
24	5	-	-	-
25	5	-	-	-
26	5	20	20	19
	Mean	19.5	19.5	19.3
	SD	-	-	-
	N	1	1	1
	%Diff	6.7	6.7	9.2

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Individual Food Consumption

(b) (4)

Key Page

Cage Contents

Cage Number	Animal Numbers	Cage Number	Animal Numbers
1	1001, 1002, 1003	2	1004, 1005, 1006
3	1007, 1008, 1009, 1010	4	1011, 1012, 1013
5	1014, 1015	6	1501, 1502, 1503, 1504, 1505
7	1506, 1507, 1508, 1509, 1510	8	1511, 1512, 1513, 1514, 1515
9	2001, 2002, 2003	10	2004, 2005, 2006
11	2007, 2008, 2009, 2010	12	2501, 2502, 2503, 2504, 2505
13	2506, 2507, 2508, 2509, 2510	14	3001, 3002, 3003
15	3004, 3005, 3006	16	3007, 3008, 3009, 3010
17	3501, 3502, 3503, 3504, 3505	18	3506, 3507, 3508, 3509, 3510
19	4001, 4002, 4003	20	4004, 4005, 4006
21	4007, 4008, 4009, 4010	22	4011, 4012, 4013
23	4014, 4015	24	4501, 4502, 4503, 4504, 4505
25	4506, 4507, 4508, 4509, 4510	26	4511, 4512, 4513, 4514, 4515

Measurement Descriptions

Headings Used	Description
Daily Food Cons Per Animal	Mean Daily Food Cons. Per Animal

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Individual Food Consumption

(b) (4)

Key Page

Measurement/Statistics

Measurement	Descriptive
Daily Food Cons Per Animal	Mean
	Standard Deviation
	Count
	% Difference from Control

Group Information

Short Name	Long Name	Type	Report Headings 1-4			
1	1:0 mg/kg/day	Control	0	mg/kg	/day	Group 1
2	2:500 mg/kg/day	Dose	500	mg/kg	/day	Group 2
3	3:1000 mg/kg/day	Dose	1000	mg/kg	/day	Group 3
4	4:2000 mg/kg/day	Dose	2000	mg/kg	/day	Group 4

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 9

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Individual Neurobehavioral Evaluation: Activity

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Activity					
		Arousal/ Alertness	Posture/ BodyCarriage	Stereotypy (HC)	Stereotypy (OF)	Rearing	Appearance
1001	85 (Pre)	0	0	0	0	11	0
1002	85 (Pre)	0 [a]	0	0	0	10	0
1003	85 (Pre)	0 [b]	0	0	0	2	0
1004	85 (Pre)	0 [c]	0	0	0	4	0
1005	85 (Pre)	0 [d]	0	0	0	3	0

[a] [RC:The animal walked on the rim of the open field for approximately 20 sec]
[b] [RC:The animal walked on the rim of the open field for approximately 01 minute et 44 secondes]
[c] [RC:The animal walked on the rim of the open field for approximately 1min17sec]
[d] [RC:The animal walked on the rim of the open field for approximately 00 minute 57 seconds]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 9

20-Feb-2023 08:55:50

Individual Neurobehavioral Evaluation: Activity

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Activity					
		Arousal/ Alertness	Posture/ BodyCarriage	Stereotypy (HC)	Stereotypy (OF)	Rearing	Appearance
2001	85 (Pre)	0	0	0	0	5	0
2002	85 (Pre)	-1 [a]	0	0	0	1	0
2003	85 (Pre)	0	0	0	0	12	0
2004	85 (Pre)	0	0	0	0	11	0
2005	85 (Pre)	0 [b]	0	0	0	1	0

[a] [RC:The animal had a freezing posture on the rim of the open field for approximately 1min 49sec]
[b] [RC:The animal walked on the rim of the open field for approximately 01 minute 46 seconds]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 9

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Individual Neurobehavioral Evaluation: Activity

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Activity					
		Arousal/ Alertness	Posture/ BodyCarriage	Stereotypy (HC)	Stereotypy (OF)	Rearing	Appearance
3001	85 (Pre)	0 [a]	0	0	0	4	0
3002	85 (Pre)	0	0	0	0	18	0
3003	85 (Pre)	0	0	0	0	14	0
3004	85 (Pre)	0 [b]	0	0	0	10	0
3005	85 (Pre)	0	0	0	0	19	0

[a] [RC:The animal walked on the rim of the open field for approximately 1 minute et 31 secondes]
[b] [RC:The animal walked on the rim of the open field for approximately 22sec]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 9

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Individual Neurobehavioral Evaluation: Activity

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Activity					
		Arousal/ Alertness	Posture/ BodyCarriage	Stereotypy (HC)	Stereotypy (OF)	Rearing	Appearance
4001	85 (Pre)	0	0	0	0	14	0
4002	85 (Pre)	0 [a]	0	0	0	3	0
4003	85 (Pre)	0 [b]	0	0	0	11	0
4004	85 (Pre)	0	0	0	0	7	0
4005	85 (Pre)	0 [c]	0	0	0	9	0

[a] [RC:The animal walked on the rim of the open field for approximately 1min41 sec]
[b] [RC:The animal walked on the rim of the open field for approximately 00 minute 29 seconds]
[c] [RC:The animal walked on the rim of the open field for approximately 10sec]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Activity

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Activity					
		Arousal/ Alertness	Posture/ BodyCarriage	Stereotypy (HC)	Stereotypy (OF)	Rearing	Appearance
1501	86 (Pre)	0 [a]	0	0	0	7	0
1502	86 (Pre)	0 [b]	0	0	0	1	0
1503	86 (Pre)	0 [c]	0	0	0	1	0
1504	86 (Pre)	0 [d]	0	0	0	10	0
1505	86 (Pre)	0 [e]	0	0	0	5	0

[a] [RC:The animal walked on the rim of the open field for approximately 30 sec]
[b] [RC:The animal walked on the rim of the open field for approximately 01 min 50 sec]
[c] [RC:The animal walked on the rim of the open field for approximately 01 minute30sec]
[d] [RC:The animal walked on the rim of the open field for approximately 00 min 50 sec]
[e] [RC:The animal walked on the rim of the open field for approximately 40sec]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Activity

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Activity					
		Arousal/ Alertness	Posture/ BodyCarriage	Stereotypy (HC)	Stereotypy (OF)	Rearing	Appearance
2501	86 (Pre)	0 [a]	0	0	0	4	0
2502	86 (Pre)	0 [b]	0	0	0	9	0
2503	86 (Pre)	0 [c]	0	0	0	2	0
2504	86 (Pre)	0 [d]	0	0	0	3	0
2505	86 (Pre)	0 [e]	0	0	0	10	0

[a] [RC:The animal walked on the rim of the open field for approximately 01 minute]
[b] [RC:The animal walked on the rim of the open field for approximately 00 min 36 sec]
[c] [RC:The animal walked on the rim of the open field for approximately 01minute30sec]
[d] [RC:The animal walked on the rim of the open field for approximately 01 min 30 sec]
[e] [RC:The animal walked on the rim of the open field for approximately 10sec]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 9

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Individual Neurobehavioral Evaluation: Activity

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Activity					
		Arousal/ Alertness	Posture/ BodyCarriage	Stereotypy (HC)	Stereotypy (OF)	Rearing	Appearance
3501	86 (Pre)	0	0	0	0	9	0
3502	86 (Pre)	0 [a]	0	0	0	6	0
3503	86 (Pre)	0 [b]	0	0	0	9	0
3504	86 (Pre)	0 [c]	0	0	0	5	0
3505	86 (Pre)	0 [d]	0	0	0	1	0

[a] [RC:The animal walked on the rim of the open field for approximately 01 min 10 sec]
[b] [RC:The animal walked on the rim of the open field for approximately 10sec]
[c] [RC:The animal walked on the rim of the open field for approximately 00 min 52 sec]
[d] [RC:The animal walked on the rim of the open field for approximately 01 min 50 sec]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 9

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Individual Neurobehavioral Evaluation: Activity

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Activity					
		Arousal/ Alertness	Posture/ BodyCarriage	Stereotypy (HC)	Stereotypy (OF)	Rearing	Appearance
4501	86 (Pre)	0 [a]	0	0	0	1	0
4502	86 (Pre)	0 [b]	0	0	0	5	0
4503	86 (Pre)	0 [c]	0	0	0	11	0
4504	86 (Pre)	0 [d]	0	0	0	1	0
4505	86 (Pre)	0 [e]	0	0	0	2	0

[a] [RC:The animal walked on the rim of the open field for approximately 01 minute50 sec]
[b] [RC:The animal walked on the rim of the open field for approximately 00 min 40 sec]
[c] [RC:The animal walked on the rim of the open field for approximately 01 minute]
[d] [RC:The animal walked on the rim of the open field for approximately 01 min 56 sec]
[e] [RC:The animal walked on the rim of the open field for approximately 01 min 42 sec]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 10

20-Feb-2023 08:55:50

Individual Neurobehavioral Evaluation: Excitability

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Excitability					
		Vocal-izations	Startle Response	Ease of Removal	Handling Reactivity	Convulsions (HC)	Convulsions (OF)
1001	85 (Pre)	0	0	0	0	0	0
1002	85 (Pre)	0	0	0	0	0	0
1003	85 (Pre)	0	0	0	0	0	0
1004	85 (Pre)	0	0	0	0	0	0
1005	85 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 10

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Individual Neurobehavioral Evaluation: Excitability

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Excitability					
		Vocal-izations	Startle Response	Ease of Removal	Handling Reactivity	Convulsions (HC)	Convulsions (OF)
2001	85 (Pre)	0	0	0	0	0	0
2002	85 (Pre)	0	0	0	0	0	0
2003	85 (Pre)	0	0	0	0	0	0
2004	85 (Pre)	0	0	0	0	0	0
2005	85 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 10

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Individual Neurobehavioral Evaluation: Excitability

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Excitability					
		Vocal-izations	Startle Response	Ease of Removal	Handling Reactivity	Convulsions (HC)	Convulsions (OF)
3001	85 (Pre)	0	0	0	0	0	0
3002	85 (Pre)	0	0	0	0	0	0
3003	85 (Pre)	0	0	0	0	0	0
3004	85 (Pre)	0	0	0	0	0	0
3005	85 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 10

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Individual Neurobehavioral Evaluation: Excitability

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Excitability					
		Vocal-izations	Startle Response	Ease of Removal	Handling Reactivity	Convulsions (HC)	Convulsions (OF)
4001	85 (Pre)	0	0	0	0	0	0
4002	85 (Pre)	0	0	0	0	0	0
4003	85 (Pre)	0	0	0	0	0	0
4004	85 (Pre)	0	0	0	0	0	0
4005	85 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 10

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Individual Neurobehavioral Evaluation: Excitability

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Excitability					
		Vocal-izations	Startle Response	Ease of Removal	Handling Reactivity	Convulsions (HC)	Convulsions (OF)
1501	86 (Pre)	0	0	0	0	0	0
1502	86 (Pre)	0	0	0	0	0	0
1503	86 (Pre)	0	0	0	0	0	0
1504	86 (Pre)	0	0	0	0	0	0
1505	86 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 10

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Individual Neurobehavioral Evaluation: Excitability

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Excitability					
		Vocal-izations	Startle Response	Ease of Removal	Handling Reactivity	Convulsions (HC)	Convulsions (OF)
2501	86 (Pre)	0	0	0	0	0	0
2502	86 (Pre)	0	0	0	0	0	0
2503	86 (Pre)	0	0	0	0	0	0
2504	86 (Pre)	0	0	0	0	0	0
2505	86 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 10

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Individual Neurobehavioral Evaluation: Excitability

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Excitability					
		Vocal-izations	Startle Response	Ease of Removal	Handling Reactivity	Convulsions (HC)	Convulsions (OF)
3501	86 (Pre)	0	0	0	0	0	0
3502	86 (Pre)	0	0	0	0	0	0
3503	86 (Pre)	0	0	0	0	0	0
3504	86 (Pre)	0	0	0	0	0	0
3505	86 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 10

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Individual Neurobehavioral Evaluation: Excitability

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Excitability					
		Vocal-izations	Startle Response	Ease of Removal	Handling Reactivity	Convulsions (HC)	Convulsions (OF)
4501	86 (Pre)	0	0	0	0	0	0
4502	86 (Pre)	0	0	0	0	0	0
4503	86 (Pre)	0	0	0	0	0	0
4504	86 (Pre)	0	0	0	0	0	0
4505	86 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 11

20-Feb-2023 08:55:50

Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Autonomic					
		Exophthalmus	Lacrimation	Palpebral Closure (HC)	Palpebral Closure (OF)	Erected Fur	Pupil Response
1001	85 (Pre)	0	0	0	0	0	0
1002	85 (Pre)	0	0	0	0	0	0
1003	85 (Pre)	0	0	0	0	0	0
1004	85 (Pre)	0	0	0	0	0	0
1005	85 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 11

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Autonomic	
		Salivation	Defecation
1001	85 (Pre)	0	-1
1002	85 (Pre)	0	-1
1003	85 (Pre)	0	-1
1004	85 (Pre)	0	-1
1005	85 (Pre)	0	-1

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 11

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Autonomic					
		Exophthalmus	Lacrimation	Palpebral Closure (HC)	Palpebral Closure (OF)	Erected Fur	Pupil Response
2001	85 (Pre)	0	0	0	0	0	0
2002	85 (Pre)	0	0	0	0	0	0
2003	85 (Pre)	0	0	0	0	0	0
2004	85 (Pre)	0	0	0	0	0	0
2005	85 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 11

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Autonomic	
		Salivation	Defecation
2001	85 (Pre)	0	-1
2002	85 (Pre)	0	-1
2003	85 (Pre)	0	-1
2004	85 (Pre)	0	-1
2005	85 (Pre)	0	0

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 11

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Autonomic					
		Exophthalmus	Lacrimation	Palpebral Closure (HC)	Palpebral Closure (OF)	Erected Fur	Pupil Response
3001	85 (Pre)	0	0	0	0	0	0
3002	85 (Pre)	0	0	0	0	0	0
3003	85 (Pre)	0	0	0	0	0	0
3004	85 (Pre)	0	0	0	0	0	0
3005	85 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Autonomic	
		Salivation	Defecation
3001	85 (Pre)	0	0
3002	85 (Pre)	0	-1
3003	85 (Pre)	0	-1 [a]
3004	85 (Pre)	0	-1
3005	85 (Pre)	0	-1

[a] [RC:Feces, Abnormal Consistency Liquides]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Autonomic					
		Exophthalmus	Lacrimation	Palpebral Closure (HC)	Palpebral Closure (OF)	Erected Fur	Pupil Response
4001	85 (Pre)	0	0	0	0	0	0
4002	85 (Pre)	0	0	0	0	0	0
4003	85 (Pre)	0	0	0	0	0	0
4004	85 (Pre)	0	0	0	0	0	0
4005	85 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Autonomic	
		Salivation	Defecation
4001	85 (Pre)	0	-1
4002	85 (Pre)	0	-1
4003	85 (Pre)	0	0
4004	85 (Pre)	0	-1
4005	85 (Pre)	0	-1

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Autonomic					
		Exophthalmus	Lacrimation	Palpebral Closure (HC)	Palpebral Closure (OF)	Erected Fur	Pupil Response
1501	86 (Pre)	0	0	0	0	0	0
1502	86 (Pre)	0	0	0	0	0	0
1503	86 (Pre)	0	0	0	0	0	0
1504	86 (Pre)	0	0	0	0	0	0
1505	86 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Autonomic	
		Salivation	Defecation
1501	86 (Pre)	0	-1
1502	86 (Pre)	0	-1
1503	86 (Pre)	0	-1
1504	86 (Pre)	0	-1
1505	86 (Pre)	0	0

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Autonomic					
		Exophthalmus	Lacrimation	Palpebral Closure (HC)	Palpebral Closure (OF)	Erected Fur	Pupil Response
2501	86 (Pre)	0	0	0	0	0	0
2502	86 (Pre)	0	0	0	0	0	0
2503	86 (Pre)	0	0	0	0	0	0
2504	86 (Pre)	0	0	0	0	0	0
2505	86 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Autonomic	
		Salivation	Defecation
2501	86 (Pre)	0	-1
2502	86 (Pre)	0	-1
2503	86 (Pre)	0	-1
2504	86 (Pre)	0	-1
2505	86 (Pre)	0	-1

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Autonomic					
		Exophthalmus	Lacrimation	Palpebral Closure (HC)	Palpebral Closure (OF)	Erected Fur	Pupil Response
3501	86 (Pre)	0	0	0	0	0	0
3502	86 (Pre)	0	0	0	0	0	0
3503	86 (Pre)	0	0	0	0	0	0
3504	86 (Pre)	0	0	0	0	0	0
3505	86 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Autonomic	
		Salivation	Defecation
3501	86 (Pre)	0	-1
3502	86 (Pre)	0	-1
3503	86 (Pre)	0	0
3504	86 (Pre)	0	-1
3505	86 (Pre)	0	-1

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 11

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Autonomic					
		Exophthalmus	Lacrimation	Palpebral Closure (HC)	Palpebral Closure (OF)	Erected Fur	Pupil Response
4501	86 (Pre)	0	0	0	0	0	0
4502	86 (Pre)	0	0	0	0	0	0
4503	86 (Pre)	0	0	0	0	0	0
4504	86 (Pre)	0	0	0	0	0	0
4505	86 (Pre)	0	0	0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Autonomic

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Autonomic	
		Salivation	Defecation
4501	86 (Pre)	0	-1
4502	86 (Pre)	0	-1
4503	86 (Pre)	0	-1
4504	86 (Pre)	0	-1
4505	86 (Pre)	0	-1

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

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Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Neuromuscular					
		Gait/ Mobility	Forelimb Grip Mean	Hindlimb Grip Mean	Air Righting Reflex	Tremor (HC)	Tremor (OF)
1001	85 (Pre)	0	1155.7	514.7	0	0	0
1002	85 (Pre)	0	824.0	335.3	0	0	0
1003	85 (Pre)	0	1361.7	527.3	0	0	0
1004	85 (Pre)	0	608.3	447.0	0	0	0
1005	85 (Pre)	0	1319.0	628.7	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

20-Feb-2023 08:56:21

Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Neuromuscular
		Body Tone
1001	85 (Pre)	0
1002	85 (Pre)	0
1003	85 (Pre)	0
1004	85 (Pre)	0
1005	85 (Pre)	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

20-Feb-2023 08:56:21

Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Neuromuscular					
		Gait/ Mobility	Forelimb Grip Mean	Hindlimb Grip Mean	Air Right ing Reflex	Tremor (HC)	Tremor (OF)
2001	85 (Pre)	0	1018.7	498.7	0	0	0
2002	85 (Pre)	0	1423.7	480.3	1 [a]	0	0
2003	85 (Pre)	0	1284.7	543.0	0	0	0
2004	85 (Pre)	0	1427.7	724.7	0	0	0
2005	85 (Pre)	0	1601.3	430.7	0	0	0

[a] [RC:Animal felt on his back and rolled over the cushion before going back on his limbs.]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

20-Feb-2023 08:56:21

Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Neuromuscular
		Body Tone
2001	85 (Pre)	0
2002	85 (Pre)	0
2003	85 (Pre)	0
2004	85 (Pre)	0
2005	85 (Pre)	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

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Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Neuromuscular					
		Gait/ Mobility	Forelimb Grip Mean	Hindlimb Grip Mean	Air Righting Reflex	Tremor (HC)	Tremor (OF)
3001	85 (Pre)	0	1205.3	476.0	0	0	0
3002	85 (Pre)	0	618.0	509.0	0	0	0
3003	85 (Pre)	0	1405.3	508.7	0	0	0
3004	85 (Pre)	0	914.3	352.3	0	0	0
3005	85 (Pre)	0	801.3	448.3	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

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Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Neuromuscular
		Body Tone
3001	85 (Pre)	0
3002	85 (Pre)	0
3003	85 (Pre)	0
3004	85 (Pre)	0
3005	85 (Pre)	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Neuromuscular					
		Gait/ Mobility	Forelimb Grip Mean	Hindlimb Grip Mean	Air Right ing Reflex	Tremor (HC)	Tremor (OF)
4001	85 (Pre)	0	1254.0	498.0	0	0	0
4002	85 (Pre)	0	1199.3	359.3	0	0	0
4003	85 (Pre)	0	1213.7	428.7	0	0	0
4004	85 (Pre)	0	1072.0	287.7	0	0	0
4005	85 (Pre)	0	612.0	249.0	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

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Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Neuromuscular
		Body Tone
4001	85 (Pre)	0
4002	85 (Pre)	0
4003	85 (Pre)	0
4004	85 (Pre)	0
4005	85 (Pre)	0

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 12

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Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Neuromuscular					
		Gait/ Mobility	Forelimb Grip Mean	Hindlimb Grip Mean	Air Righting Reflex	Tremor (HC)	Tremor (OF)
1501	86 (Pre)	0	363.7	588.3	0	0	0
1502	86 (Pre)	0	1122.7	451.0	0	0	0
1503	86 (Pre)	0	505.3	416.0	0	0	0
1504	86 (Pre)	0	1599.3	509.7	0	0	0
1505	86 (Pre)	0	546.0	501.7	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

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Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Neuromuscular
		Body Tone
1501	86 (Pre)	0
1502	86 (Pre)	0
1503	86 (Pre)	0
1504	86 (Pre)	0
1505	86 (Pre)	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

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Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Neuromuscular					
		Gait/ Mobility	Forelimb Grip Mean	Hindlimb Grip Mean	Air Righting Reflex	Tremor (HC)	Tremor (OF)
2501	86 (Pre)	0	722.3	594.3	0	0	0
2502	86 (Pre)	0	1371.7	483.7	0	0	0
2503	86 (Pre)	0	498.7	459.7	0	0	0
2504	86 (Pre)	0	1283.7	597.7	0	0	0
2505	86 (Pre)	0	755.0	444.7	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

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Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Neuromuscular
		Body Tone
2501	86 (Pre)	0
2502	86 (Pre)	0
2503	86 (Pre)	0
2504	86 (Pre)	0
2505	86 (Pre)	0

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 12

20-Feb-2023 08:56:21

Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Neuromuscular					
		Gait/ Mobility	Forelimb Grip Mean	Hindlimb Grip Mean	Air Righting Reflex	Tremor (HC)	Tremor (OF)
3501	86 (Pre)	0	599.0	386.0	0	0	0
3502	86 (Pre)	0	1105.0	525.7	0	0	0
3503	86 (Pre)	0	828.0	343.3	0	0	0
3504	86 (Pre)	0	1369.0	492.0	0	0	0
3505	86 (Pre)	0	986.0	441.7	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

20-Feb-2023 08:56:21

Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Neuromuscular
		Body Tone
3501	86 (Pre)	0
3502	86 (Pre)	0
3503	86 (Pre)	0
3504	86 (Pre)	0
3505	86 (Pre)	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

20-Feb-2023 08:56:21

Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Neuromuscular					
		Gait/ Mobility	Forelimb Grip Mean	Hindlimb Grip Mean	Air Right ing Reflex	Tremor (HC)	Tremor (OF)
4501	86 (Pre)	0	705.0	413.0	0	0	0
4502	86 (Pre)	0	985.0	455.7	0	0	0
4503	86 (Pre)	0	489.0	322.7	0	0	0
4504	86 (Pre)	0	1028.0	479.0	0	0	0
4505	86 (Pre)	0	1231.3	548.3	0	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 12

20-Feb-2023 08:56:21

Individual Neurobehavioral Evaluation: Neuromuscular

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Neuromuscular
		Body Tone
4501	86 (Pre)	0
4502	86 (Pre)	0
4503	86 (Pre)	0
4504	86 (Pre)	0
4505	86 (Pre)	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 13

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Sensorimotor

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Sensorimotor	
		Touch Resp/ Tactile Refl	Tail Pinch Response
1001	85 (Pre)	0	0
1002	85 (Pre)	0	0
1003	85 (Pre)	0	0
1004	85 (Pre)	0	0
1005	85 (Pre)	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 13

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Sensorimotor

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Sensorimotor	
		Touch Resp/ Tactile Refl	Tail Pinch Response
2001	85 (Pre)	0	0
2002	85 (Pre)	0	0
2003	85 (Pre)	0	0
2004	85 (Pre)	0	0
2005	85 (Pre)	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 13

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Sensorimotor

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Sensorimotor	
		Touch Resp/ Tactile Refl	Tail Pinch Response
3001	85 (Pre)	0	0
3002	85 (Pre)	0	0 [a]
3003	85 (Pre)	0	0
3004	85 (Pre)	0	0
3005	85 (Pre)	0	0

[a] [RC:Feces, Abnormal Consistency Soft]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 13

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Sensorimotor

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Sensorimotor	
		Touch Resp/ Tactile Refl	Tail Pinch Response
4001	85 (Pre)	0	0
4002	85 (Pre)	0	0
4003	85 (Pre)	0	0
4004	85 (Pre)	0	0
4005	85 (Pre)	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 13

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Sensorimotor

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Sensorimotor	
		Touch Resp/ Tactile Refl	Tail Pinch Response
1501	86 (Pre)	0	0
1502	86 (Pre)	0	0
1503	86 (Pre)	0	0
1504	86 (Pre)	0	0
1505	86 (Pre)	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 13

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Sensorimotor

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Sensorimotor	
		Touch Resp/ Tactile Refl	Tail Pinch Response
2501	86 (Pre)	0	0
2502	86 (Pre)	0	0
2503	86 (Pre)	0	0
2504	86 (Pre)	0	0
2505	86 (Pre)	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 13

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Sensorimotor

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Sensorimotor	
		Touch Resp/ Tactile Refl	Tail Pinch Response
3501	86 (Pre)	0	0
3502	86 (Pre)	0	0
3503	86 (Pre)	0	0
3504	86 (Pre)	0	0
3505	86 (Pre)	0	-1

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 13

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Sensorimotor

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Sensorimotor	
		Touch Resp/ Tactile Refl	Tail Pinch Response
4501	86 (Pre)	0	0
4502	86 (Pre)	0	-1
4503	86 (Pre)	0	0
4504	86 (Pre)	0	0
4505	86 (Pre)	0	0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 14

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Physiological

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Physiological	
		Respiration	Body Temperature (oC)
1001	85 (Pre)	0	36.4
1002	85 (Pre)	0	35.4
1003	85 (Pre)	0	38.1 [a]
1004	85 (Pre)	0	36.6
1005	85 (Pre)	0	36.2

[a] [RC:Feces, Abnormal Consistency Mucoïdes]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 14

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Physiological

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Physiological	
		Respiration	Body Temperature (oC)
2001	85 (Pre)	0	36.5
2002	85 (Pre)	0	35.7
2003	85 (Pre)	0	37.1
2004	85 (Pre)	0	35.6
2005	85 (Pre)	0	37.4

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 14

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Physiological

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Physiological	
		Respiration	Body Temperature (oC)
3001	85 (Pre)	0	35.8
3002	85 (Pre)	0	35.5
3003	85 (Pre)	0	36.1
3004	85 (Pre)	0	36.7
3005	85 (Pre)	0	35.1

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 14

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Physiological

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Physiological	
		Respiration	Body Temperature (oC)
4001	85 (Pre)	0	36.7
4002	85 (Pre)	0	36.5
4003	85 (Pre)	0	36.4
4004	85 (Pre)	0	36.0
4005	85 (Pre)	0	36.0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 14

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Physiological

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Physiological	
		Respiration	Body Temperature (oC)
1501	86 (Pre)	0	37.5
1502	86 (Pre)	0	38.0
1503	86 (Pre)	0	36.2
1504	86 (Pre)	0	38.2
1505	86 (Pre)	0	36.7

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 14

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Physiological

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Physiological	
		Respiration	Body Temperature (oC)
2501	86 (Pre)	0	36.3
2502	86 (Pre)	0	37.8
2503	86 (Pre)	0	36.1
2504	86 (Pre)	0	37.7
2505	86 (Pre)	0	36.0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 14

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Physiological

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Physiological	
		Respiration	Body Temperature (oC)
3501	86 (Pre)	0	36.4
3502	86 (Pre)	0	37.9
3503	86 (Pre)	0	37.4
3504	86 (Pre)	0	38.2
3505	86 (Pre)	0	37.0

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 14

20-Feb-2023 08:56:19

Individual Neurobehavioral Evaluation: Physiological

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Physiological	
		Respiration	Body Temperature (oC)
4501	86 (Pre)	0	36.1
4502	86 (Pre)	0	38.4
4503	86 (Pre)	0	37.2
4504	86 (Pre)	0	37.6
4505	86 (Pre)	0	37.5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 15

SCORING CRITERIA FOR THE NEUROBEHAVIORAL ASSESSMENT (1/3)

Activity Domain		
Arousal/Alertness	-2	Very low (stuporous, comatose, little to no movement)
	-1	Low (sluggish, some exploratory movement)
	0	Normal (alert with exploratory movement)
	1	High (tense, some bouts of startle, darting, or freezing without stimuli)
	2	Very High (excited, multiple bouts of startle, running, darting, freezing, or body movements without stimuli)
Posture/Body Carriage	-2	Prostrate (limbs may be in the air) or flattened to cage floor (limbs may be spread out)
	-1	Hunched or low carriage
	0	Normal; Asleep/lying down, sitting or standing normally
Stereotypy	0	Not present; Normal
	1	Continuous licking, biting/gnawing of the wall or floor, continuous or excessive grooming
	2	Repetitive mouth movements, and/or head weaving/bobbing
	3	Circling, retropulsion, forepaw treading
	4	Self-Injurious behavior; Licking, biting, or gnawing of the body
Number of Rearings		Individual count
Appearance	0	Clean and groomed
	1	Slightly unkempt (slightly discolored/crusty fur)
	2	Extremely unkempt (markedly discolored, matted, and/or crusty fur)
Excitability Domain		
Vocalizations	0	Spontaneous vocalizations occur once or not at all
	1	Spontaneous vocalizations occur more than once
Startle Response	-1	No reaction
	0	Normal reaction (some evidence that the noise was heard; e.g., normal freezing, flinching, or jumping behaviors)
	1	Exaggerated reaction (e.g., excessive jumping, attacking, or vocalization)
Ease of Removal	-1	Very easy (animal is sluggish or limp)
	0	Easy (sits quietly, allows observer to pick it up with minimal resistance)
	1	Moderate (rears, often following observer's hand, vocalizations may occur)
	2	Difficult (runs around cage, is hard to grab, with or without vocalizations, tail and throat rattles, may attack hand)
Handling Reactivity	-1	Very low (animal is totally limp or otherwise unresponsive)
	0	Low (minimal resistance, is easy to handle)
	1	Moderate (slight resistance)
	2	High (may freeze, be tense, or rigid in hand, squirming, twisting, or attempting to bite)
Convulsions	0	None
	1	Clonic movement of limbs, ears, head, or skin, repetitive movements of mouth and jaw; Contraction of extensors such that limbs are rigid, extended
	2	Clonic tremors or clonus of the limbs or whole body; Opisthotonus (head and body rigidly arched backwards) or emprosthotonus (head and body rigidly extended forward)
	3	Severe clonus of the limbs or whole body; Myoclonic jerks; Explosive jumps into the air with all feet leaving surface
	4	Clonic convulsions affecting the whole body; Clonic-tonic convulsions, possibly resulting in dyspnea, or death

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 15

SCORING CRITERIA FOR THE NEUROBEHAVIORAL ASSESSMENT (2/3)

Autonomic Domain		
Exophtalmus	**0**	Not present
	1	Present
Lacrimation	**0**	None (no excess lacrimation)
	1	Slight (excess moisture at the margin of the eyelid)
	2	Severe (dampness extends beyond the margin of the eyelid)
Erected Fur (Piloerection)	**0**	Not present
	1	Present (coat does not lie down after stroking)
Pupil Response	**0**	Normal constriction of pupils
	1	Partial, slow, or lack of constriction of pupils
	2	Pupils are fully constricted prior to performing the test (i.e., "pinpoint pupils")
Salivation	**0**	None (no excess salivation)
	1	Slight (margin of mouth wet)
	2	Severe (wet zone extends beyond the margin of the mouth)
Defecation	**-1**	Absent
	0	Normal
	1	Abnormal
Palpebral Closure/Ptosis	**0**	Eyelids wide open
	1	Eyelids drooping approximately half-way
	2	Eyelids completely shut
Neuromuscular Domain		
Gait/Mobility	**0**	Normal gait/mobility
	1	Slightly impaired (i.e., any or all of the following may be evident): mild ataxia, rocks or lurches during ambulation; hunched or crouched body position; walks on tiptoe
	2	Moderately impaired (i.e., any or all of the following may be evident): marked ataxia; feet point outwards from the body; hind limbs show exaggerated or overcompensated movements, drag, or are splayed
	3	Severely impaired (i.e., any or all of the following may be evident): Forelimbs drag or are unable to support weight; body drags or is flattened against surface
Grip Strength (in Grams)	Three individual measurements	
Air Righting Reflex	**0**	Normal (animal lands on four feet)
	1	Abnormal
	2	Animal severely impaired (not tested)
Tremors	**0**	None
	1	Slight (barely perceptible)
	2	Moderate (apparent, but still able to perform other activities)
	3	Severe (impairs general activity)
Body Tone	**-1**	Decreased (flaccidity)
	0	Normal
	1	Increased (resistance to palpation; rigidity)

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 15

SCORING CRITERIA FOR THE NEUROBEHAVIORAL ASSESSMENT (3/3)

Sensorimotor Domain		
Touch Response/Tactile Reflex	**-1**	No reaction
	0	Normal reaction (may turn towards or away from stimulus)
	1	Exaggerated reaction (freezes or flinches, jumps, bites, or attacks)
Tail Pinch Response	**-1**	No reaction
	0	Normal reaction (some evidence that the pinch was noted e.g., normal flinching, jumping behaviors or vocalization)
	1	Exaggerated reaction (e.g., excessive jumping, attacking, or vocalization)
Physiological Domain		
Respiration	**-1**	Slowed
	0	Normal
	1	Rapid
	2	Abnormal
Body Temperature (in °C)		

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 16

Motor Activity - Fine Movements (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13
Males

Group 1, 0 mg/kg/day

Animal Number	Interval										Total
	1	2		3		4		5		6	
1001	459	352	-23%	296	-36%	42	-91%	165	-64%	396	-14%	1710
1002	820	779	-5%	258	-69%	20	-98%	468	-43%	659	-20%	3004
1003	436	440	1%	360	-17%	198	-55%	316	-28%	334	-23%	2084
1004	707	540	-24%	271	-62%	229	-68%	156	-78%	368	-48%	2271
1005	493	353	-28%	223	-55%	160	-68%	501	2%	64	-87%	1794
Mean	583	493	-16%	282	-48%	130	-76%	321	-42%	364	-38%	2173
SD	171	178	13	51	21	94	18	162	31	212	30	516
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 2, 500 mg/kg/day

Animal Number	Interval										Total
	1	2		3		4		5		6	
2001	1343	918	-32%	659	-51%	212	-84%	474	-65%	160	-88%	3766
2002	614	458	-25%	36	-94%	190	-69%	380	-38%	439	-29%	2117
2003	906	617	-32%	229	-75%	117	-87%	6	-99%	296	-67%	2171
2004	1253	504	-60%	1	-100%	320	-74%	599	-52%	109	-91%	2786
2005	743	286	-62%	323	-57%	37	-95%	142	-81%	40	-95%	1571
Mean	972	557	-42%	250	-75%	175	-82%	320	-67%	209	-74%	2482
SD	317	235	17	265	22	106	10	243	24	159	28	837
N	5	5	5	5	5	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 16

Motor Activity - Fine Movements (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13
Males

Group 3, 1000 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
3001	730	321	-56%	292	-60%	371	-49%	40	-95%	218	-70%	1972
3002	696	372	-47%	407	-42%	287	-59%	502	-28%	186	-73%	2450
3003	613	530	-14%	499	-19%	381	-38%	493	-20%	386	-37%	2902
3004	829	683	-18%	466	-44%	332	-60%	399	-52%	598	-28%	3307
3005	588	506	-14%	109	-81%	390	-34%	206	-65%	241	-59%	2040
Mean	691	482	-30%	355	-49%	352	-48%	328	-52%	326	-53%	2534
SD	97	143	20	158	23	43	12	200	30	170	20	570
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 4, 2000 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
4001	1118	508	-55%	778	-30%	299	-73%	507	-55%	726	-35%	3936
4002	908	514	-43%	372	-59%	672	-26%	938	3%	853	-6%	4257
4003	1251	532	-57%	354	-72%	347	-72%	751	-40%	421	-66%	3656
4004	1204	409	-66%	698	-42%	679	-44%	119	-90%	345	-71%	3454
4005	682	586	-14%	462	-32%	421	-38%	436	-36%	414	-39%	3001
Mean	1033	510	-47%	533	-47%	484	-51%	550	-44%	552	-44%	3661
SD	236	64	20	194	18	181	21	313	34	224	26	477
N	5	5	5	5	5	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 16

Motor Activity - Fine Movements (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13
Females

Group 1, 0 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
1501	477	381	-20%	324	-32%	79	-83%	261	-45%	432	-9%	1954
1502	989	750	-24%	829	-16%	439	-56%	23	-98%	517	-48%	3547
1503	930	340	-63%	577	-38%	92	-90%	25	-97%	470	-49%	2434
1504	778	465	-40%	669	-14%	184	-76%	51	-93%	8	-99%	2155
1505	574	559	-3%	514	-10%	32	-94%	8	-99%	2	-100%	1689
Mean	750	499	-30%	583	-22%	165	-80%	74	-86%	286	-61%	2356
SD	221	164	23	187	12	163	15	106	23	258	38	720
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 2, 500 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
2501	449	338	-25%	49	-89%	7	-98%	321	-29%	333	-26%	1497
2502	797	506	-37%	382	-52%	382	-52%	48	-94%	37	-95%	2152
2503	659	345	-48%	354	-46%	152	-77%	367	-44%	71	-89%	1948
2504	941	340	-64%	181	-81%	412	-56%	27	-97%	308	-67%	2209
2505	447	464	4%	278	-38%	19	-96%	408	-9%	7	-98%	1623
Mean	659	399	-34%	249	-61%	194	-76%	234	-55%	151	-75%	1886
SD	217	80	25	136	22	194	22	182	40	156	30	316
N	5	5	5	5	5	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 16

Motor Activity - Fine Movements (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13
Females

Group 3, 1000 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
3501	662	441	-33%	868	31%	46	-93%	107	-84%	32	-95%	2156
3502	628	411	-35%	14	-98%	30	-95%	67	-89%	39	-94%	1189
3503	704	569	-19%	452	-36%	46	-93%	107	-85%	118	-83%	1996
3504	532	420	-21%	259	-51%	123	-77%	137	-74%	353	-34%	1824
3505	596	590	-1%	225	-62%	294	-51%	29	-95%	96	-84%	1830
Mean	624	486	-22%	364	-43%	108	-82%	89	-85%	128	-78%	1799
SD	65	86	14	322	47	110	19	42	8	131	25	367
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 4, 2000 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
4501	457	110	-76%	399	-13%	229	-50%	443	-3%	79	-83%	1717
4502	533	627	18%	475	-11%	15	-97%	68	-87%	81	-85%	1799
4503	658	438	-33%	166	-75%	230	-65%	590	-10%	362	-45%	2444
4504	595	416	-30%	802	35%	184	-69%	266	-55%	293	-51%	2556
4505	863	658	-24%	737	-15%	689	-20%	148	-83%	522	-40%	3617
Mean	621	450	-29%	516	-16%	269	-60%	303	-48%	267	-61%	2427
SD	154	219	33	259	39	251	28	214	40	190	22	763
N	5	5	5	5	5	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 16

Motor Activity - Ambulation (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13
Males

Group 1, 0 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
1001	71	45	-37%	39	-45%	0	-100%	22	-69%	51	-28%	228
1002	243	200	-18%	36	-85%	0	-100%	82	-66%	164	-33%	725
1003	18	7	-61%	17	-6%	6	-67%	51	183%	5	-72%	104
1004	182	104	-43%	35	-81%	43	-76%	25	-86%	65	-64%	454
1005	26	17	-35%	9	-65%	1	-96%	30	15%	4	-85%	87
Mean	108	75	-39%	27	-56%	10	-88%	42	-5%	58	-56%	320
SD	100	80	16	13	32	19	15	25	112	65	25	270
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 2, 500 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
2001	384	183	-52%	135	-65%	68	-82%	62	-84%	25	-93%	857
2002	165	81	-51%	0	-100%	19	-88%	87	-47%	87	-47%	439
2003	257	129	-50%	49	-81%	8	-97%	1	-100%	77	-70%	521
2004	290	86	-70%	0	-100%	55	-81%	64	-78%	2	-99%	497
2005	152	38	-75%	58	-62%	0	-100%	0	-100%	0	-100%	248
Mean	250	103	-60%	48	-82%	30	-90%	43	-82%	38	-82%	512
SD	95	55	12	55	18	30	9	40	22	41	23	220
N	5	5	5	5	5	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 16

Motor Activity - Ambulation (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13
Males

Group 3, 1000 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
3001	206	7	-97%	87	-58%	68	-67%	0	-100%	51	-75%	419
3002	89	33	-63%	70	-21%	67	-25%	83	-7%	27	-70%	369
3003	179	90	-50%	50	-72%	128	-28%	126	-30%	105	-41%	678
3004	198	101	-49%	89	-55%	79	-60%	116	-41%	127	-36%	710
3005	125	88	-30%	7	-94%	95	-24%	57	-54%	58	-54%	430
Mean	159	64	-58%	61	-60%	87	-41%	76	-46%	74	-55%	521
SD	50	41	25	34	27	25	21	51	35	41	17	160
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 4, 2000 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
4001	284	149	-48%	157	-45%	29	-90%	129	-55%	121	-57%	869
4002	171	24	-86%	41	-76%	60	-65%	58	-66%	44	-74%	398
4003	325	52	-84%	62	-81%	19	-94%	101	-69%	56	-83%	615
4004	262	13	-95%	146	-44%	137	-48%	16	-94%	56	-79%	630
4005	109	110	1%	81	-26%	81	-26%	87	-20%	56	-49%	524
Mean	230	70	-62%	97	-54%	65	-64%	78	-61%	67	-68%	607
SD	88	58	40	52	23	47	29	43	27	31	15	173
N	5	5	5	5	5	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 16

Motor Activity - Ambulation (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13
Females

Group 1, 0 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
1501	85	132	55%	119	40%	2	-98%	58	-32%	38	-55%	434
1502	384	173	-55%	148	-61%	4	-99%	0	-100%	153	-60%	862
1503	291	95	-67%	88	-70%	3	-99%	0	-100%	103	-65%	580
1504	259	85	-67%	202	-22%	3	-99%	0	-100%	0	-100%	549
1505	137	166	21%	52	-62%	1	-99%	0	-100%	0	-100%	356
Mean	231	130	-23%	122	-35%	3	-99%	12	-86%	59	-76%	556
SD	120	40	57	57	46	1	1	26	31	67	22	193
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 2, 500 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
2501	149	83	-44%	0	-100%	0	-100%	81	-46%	84	-44%	397
2502	268	170	-37%	108	-60%	140	-48%	0	-100%	0	-100%	686
2503	200	68	-66%	36	-82%	55	-73%	78	-61%	7	-97%	444
2504	274	86	-69%	21	-92%	52	-81%	2	-99%	67	-76%	502
2505	108	130	20%	8	-93%	2	-98%	105	-3%	0	-100%	353
Mean	200	107	-39%	35	-85%	50	-80%	53	-62%	32	-83%	476
SD	73	42	36	43	16	57	21	49	41	41	24	130
N	5	5	5	5	5	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 16

Motor Activity - Ambulation (Count - Percentage of Habituation Compared to the 1st Interval) - Week 13
Females

Group 3, 1000 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
3501	227	113	-50%	156	-31%	0	-100%	0	-100%	4	-98%	500
3502	225	101	-55%	0	-100%	0	-100%	3	-99%	7	-97%	336
3503	210	109	-48%	82	-61%	0	-100%	29	-86%	15	-93%	445
3504	128	74	-42%	71	-45%	40	-69%	3	-98%	46	-64%	362
3505	167	81	-51%	44	-74%	6	-96%	0	-100%	0	-100%	298
Mean	191	96	-49%	71	-62%	9	-93%	7	-97%	14	-90%	388
SD	43	17	5	57	27	17	14	12	6	19	15	83
N	5	5	5	5	5	5	5	5	5	5	5	5

Group 4, 2000 mg/kg/day

Animal Number	Interval											Total
	1	2		3		4		5		6		
4501	79	6	-92%	84	6%	86	9%	125	58%	12	-85%	392
4502	110	243	121%	111	1%	0	-100%	3	-97%	0	-100%	467
4503	219	118	-46%	22	-90%	115	-47%	245	12%	68	-69%	787
4504	146	122	-16%	296	103%	73	-50%	86	-41%	102	-30%	825
4505	182	155	-15%	159	-13%	162	-11%	3	-98%	145	-20%	806
Mean	147	129	-10%	134	1%	87	-40%	92	-33%	65	-61%	655
SD	56	85	80	103	69	60	42	100	69	61	34	208
N	5	5	5	5	5	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 17

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Individual Ophthalmology Observations

(b) (4)

0 mg/kg /day Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-6	87					
1001	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Linear, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Linear, Right, 2 Slight, Multifocal	X	X					
1002	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Linear, Right, 2 Slight, Focal	X	X					
1003	Fundus, Pale, Left, 2 Slight	.	X					
	Fundus, Pale, Right, 2 Slight	.	X					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
1004	Iris, Persist Pupil Membrane, Left	X	.					
	Iris, Persist Pupil Membrane, Right	X	.					
	Lens Nucleus Prominent, Left	X	.					
	Lens Nucleus Prominent, Right	X	.					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
1005	Cornea, Opacity, Pinpoint, Left, 2 Slight, Focal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X	.					
	Cornea, Opacity, Linear, Left, 2 Slight, Multifocal	.	X					
1006	Cornea, Opacity, Pinpoint, Left, 2 Slight, Focal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Focal	X	X					
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X	.					

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 17

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Individual Ophthalmology Observations

(b) (4)

0 mg/kg /day Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-6	87					
1006	Cornea, Opacity, Linear, Left, 2 Slight, Multifocal	.	X					
1007	Fundus, Pale, Left, 2 Slight	.	X					
	Fundus, Pale, Right, 2 Slight	.	X					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Linear, Right, 2 Slight, Focal	X	.					
	Cornea, Opacity, Linear, Right, 2 Slight, Multifocal	.	X					
1008	Iris, Persist Pupil Membrane, Left	X	X					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Focal	X	X					
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X	X					
	Cornea, Opacity, Linear, Right, 2 Slight, Focal	X	X					
1009	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Linear, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Linear, Right, 2 Slight, Focal	X	.					
	Cornea, Opacity, Linear, Right, 2 Slight, Multifocal	.	X					
1010	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Linear, Right, 2 Slight, Focal	.	X					
1011	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X	.					
1012	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Linear, Left, 2 Slight, Multifocal	X	.					

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 17

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Individual Ophthalmology Observations

(b) (4)

0 mg/kg /day Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-6	87					
1012	Cornea, Opacity, Linear, Right, 2 Slight, Multifocal	X	.					
1013	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X	.					
	Cornea, Opacity, Linear, Right, 2 Slight, Focal	X	.					
1014	Iris, Persist Pupil Membrane, Left	X	.					
	Iris, Persist Pupil Membrane, Right	X	.					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
1015	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					

X=Present

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 17

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Individual Ophthalmology Observations

(b) (4)

500 mg/kg /day Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-6						
2001	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Right, 2 Slight, Focal	X						
2002	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
2003	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Right, 2 Slight, Multifocal	X						
2004	Cornea, Opacity, Pinpoint, Left, 2 Slight, Focal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
2005	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X						
2006	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Right, 2 Slight, Multifocal	X						
2007	Cornea, Opacity, Pinpoint, Left, 2 Slight, Focal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Focal	X						
2008	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
2009	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Right, 2 Slight, Focal	X						
2010	Iris, Persist Pupil Membrane, Right	X						
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 17

20-Feb-2023 08:42:04

Individual Ophthalmology Observations

(b) (4)

		Day(s) Relative to Start Date						
500 mg/kg /day Group 2 Sex: Male	Observation Type: All Types	-6						
2010	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Left, 2 Slight, Multifocal	X						

X=Present

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 17

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Individual Ophthalmology Observations

(b) (4)

1000 mg/kg /day Group 3 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-6						
3001	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3002	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3003	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X						
	Cornea, Opacity, Linear, Right, 2 Slight, Multifocal	X						
3004	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3005	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Right, 2 Slight, Multifocal	X						
3006	Iris, Persist Pupil Membrane, Left	X						
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X						
	Cornea, Opacity, Linear, Right, 2 Slight, Multifocal	X						
3007	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3008	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Right, 2 Slight, Focal	X						
3009	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 17

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Individual Ophthalmology Observations

(b) (4)

1000 mg/kg /day Group 3 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-6						
3009	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3010	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X						

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 17

20-Feb-2023 08:42:05

Individual Ophthalmology Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-6	87					
4001	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4002	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4003	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4004	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4005	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4006	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4007	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4008	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X	X					
	Cornea, Opacity, Linear, Right, 2 Slight, Focal	X	X					
4009	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4010	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4011	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Linear, Right, 2 Slight, Multifocal	X	.					

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 17

20-Feb-2023 08:42:05

Individual Ophthalmology Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-6	87					
4012	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X	.					
4013	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
4014	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Linear, Left, 2 Slight, Multifocal	X	.					
4015	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 17

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Individual Ophthalmology Observations

(b) (4)

0 mg/kg /day Group 1 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-6	87					
1501	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X	X					
1503	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
1504	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	.	X					
1505	Cornea, Opacity, Pinpoint, Left, 2 Slight, Focal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
1506	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
1507	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
1508	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Focal	.	X					
1509	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	.	X					
1511	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
1513	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
1515	Cornea, Opacity, Pinpoint, Left, 2 Slight, Focal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Ophthalmology Observations

(b) (4)

500 mg/kg /day Group 2 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-6						
2501	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
2502	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
2503	Iris, Persist Pupil Membrane, Left	X						
	Iris, Persist Pupil Membrane, Right	X						
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
2505	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
2506	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
2507	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
2508	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
2509	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
2510	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 17

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Individual Ophthalmology Observations

(b) (4)

1000 mg/kg /day Group 3 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-6						
3501	Iris, Persist Pupil Membrane, Right	X						
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Linear, Left, 2 Slight, Focal	X						
3502	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3503	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3504	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3505	Cornea, Opacity, Pinpoint, Left, 2 Slight, Focal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3506	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3508	Cornea, Opacity, Pinpoint, Left, 2 Slight, Focal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3509	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						
3510	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X						
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X						

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Ophthalmology Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-6	87					
4501	Iris, Persist Pupil Membrane, Left	X	X					
	Fundus, Vessels, Pale, Left, 2 Slight	.	X					
	Fundus, Pale, Left, 2 Slight	.	X					
	Fundus, Pale, Right, 2 Slight	.	X					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4502	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4503	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4504	Fundus, Pale, Left, 2 Slight	.	X					
	Fundus, Pale, Right, 2 Slight	.	X					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4505	Fundus, Pale, Left, 2 Slight	.	X					
	Fundus, Pale, Right, 2 Slight	.	X					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4506	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4507	Fundus, Pale, Left, 2 Slight	.	X					
	Fundus, Pale, Right, 2 Slight	.	X					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	.	X					

X=Present

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Ophthalmology Observations

(b) (4)

2000 mg/kg /day Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-6	87					
4508	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
4509	Fundus, Pale, Left, 2 Slight	.	X					
	Fundus, Pale, Right, 2 Slight	.	X					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4510	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	X					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	X					
4511	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
4512	Iris, Persist Pupil Membrane, Left	X	.					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
4513	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
4514	Iris, Persist Pupil Membrane, Left	X	.					
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					
4515	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	X	.					
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	X	.					

X=Present

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Hematology					
		WBC (10^9/L)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BASO (%)
1001	91	4.61	35.7	60.3	2.5	1.3	0.1
1002	91	4.48	39.7	55.1	3.3	1.3	0.1
1003	91	6.33	49.0	47.2	2.5	1.0	0.1
1004	91	3.90	43.2	53.8	1.9	0.9	0.1
1005	91	4.54	41.2	54.9	1.9	1.2	0.2
1006	92	6.72	47.5	48.3	2.5	1.4	0.1
1007	92	4.44	32.3	61.1	3.3	2.9	0.2
1008	92	6.36	63.7	31.7	2.8	1.5	0.1
1009	92	7.36	41.0	54.2	2.1	2.0	0.3
1010	92	7.36	49.5	44.8	3.5	1.9	0.2
1011	120	3.37	43.8	53.1	1.7	1.0	0.1
1012	120	5.54	41.7	55.0	1.8	1.2	0.0
1013	120	3.71	42.0	53.1	2.6	1.7	0.1
1014	120	4.81	33.3	62.0	3.7	0.7	0.1
1015	120	6.82	34.8	62.4	1.7	0.8	0.1

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Individual Hematology Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (%)	NEUT (10^9/L)	LYMPH (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
1001	91	0.1	1.64	2.78	0.11	0.06	0.01
1002	91	0.5	1.78	2.47	0.15	0.06	0.00
1003	91	0.2	3.10	2.99	0.16	0.06	0.01
1004	91	0.2	1.68	2.10	0.07	0.04	0.00
1005	91	0.5	1.87	2.50	0.09	0.05	0.01
1006	92	0.2	3.19	3.25	0.17	0.09	0.01
1007	92	0.2	1.44	2.72	0.14	0.13	0.01
1008	92	0.2	4.05	2.02	0.18	0.09	0.01
1009	92	0.4	3.02	3.99	0.15	0.15	0.02
1010	92	0.2	3.64	3.29	0.26	0.14	0.01
1011	120	0.2	1.48	1.79	0.06	0.03	0.00
1012	120	0.3	2.31	3.05	0.10	0.06	0.00
1013	120	0.6	1.56	1.97	0.10	0.06	0.00
1014	120	0.2	1.60	2.98	0.18	0.03	0.01
1015	120	0.3	2.37	4.25	0.11	0.05	0.01

Sponsor Reference No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (10^9/L)	RBC (10^12/L)	HGB (g/L)	HCT (L/L)	MCV (fL)	MCH (pg)
1001	91	0.01	7.40	134	0.414	55.9	18.2
1002	91	0.02	6.84	128	0.371	54.2	18.6
1003	91	0.01	7.55	132	0.389	51.5	17.5
1004	91	0.01	6.73	126	0.379	56.3	18.7
1005	91	0.02	6.85	128	0.368	53.7	18.6
1006	92	0.01	7.57	127	0.390	51.5	16.8
1007	92	0.01	8.45	148	0.449	53.2	17.5
1008	92	0.01	7.86	131	0.412	52.4	16.7
1009	92	0.03	7.88	133	0.413	52.5	16.9
1010	92	0.02	7.68	136	0.425	55.3	17.8
1011	120	0.01	7.37	125	0.383	52.0	16.9
1012	120	0.02	7.89	130	0.397	50.3	16.5
1013	120	0.02	6.96	127	0.377	54.1	18.2
1014	120	0.01	7.48	145	0.436	58.3	19.4
1015	120	0.02	7.39	132	0.387	52.3	17.8

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Individual Hematology Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Hematology					
		MCHC (g/L)	RDWG (%)	PLT (10^9/L)	MPV (fL)	RETIC (10^9/L)	RETIC (%)
1001	91	325	12.6	785	8.9	235.3	3.2
1002	91	343	12.3	620	8.6	153.7	2.2
1003	91	340	12.3	732	8.3	172.7	2.3
1004	91	331	13.1	555	9.2	184.0	2.7
1005	91	347	14.8	586	8.4	138.5	2.0
1006	92	326	13.1	692	7.8	175.6	2.3
1007	92	330	12.8	726	8.1	222.1	2.6
1008	92	319	13.2	704	8.0	193.2	2.5
1009	92	323	13.3	782	7.7	170.0	2.2
1010	92	322	12.3	650	8.2	193.4	2.5
1011	120	326	13.0	649	9.4	199.6	2.7
1012	120	328	13.2	645	9.2	167.3	2.1
1013	120	336	12.2	573	9.7	140.1	2.0
1014	120	334	12.1	625	9.4	194.8	2.6
1015	120	341	12.1	553	9.6	180.7	2.4

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Individual Hematology Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Hematology			
		POLY	ROULEAUX	PLATELET CLUMPS	WBC MORPH
1001	91	-	-	-	-
1002	91	-	-	-	-
1003	91	-	-	-	-
1004	91	-	-	-	-
1005	91	-	-	-	-
1006	92	-	-	-	-
1007	92	-	-	-	-
1008	92	-	-	-	-
1009	92	-	-	-	-
1010	92	-	-	-	-
1011	120	-	-	-	-
1012	120	-	-	-	-
1013	120	-	-	-	-
1014	120	-	-	-	-
1015	120	-	-	-	-

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Hematology					
		WBC (10^9/L)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BASO (%)
2001	91	4.78	53.3	40.3	4.7	1.2	0.2
2002	91	6.43	33.9	61.0	3.0	1.6	0.0
2003	91	4.54	40.5	55.0	2.5	1.7	0.1
2004	91	5.79	37.9	56.8	2.8	2.2	0.1
2005	91	7.12	27.8	65.8	3.1	2.0	0.1
2006	92	4.94	42.4	52.1	2.9	1.7	0.2
2007	92	5.46	44.4	51.0	2.9	1.2	0.2
2008	92	2.62	36.9	57.1	1.8	3.8	0.2
2009	92	5.76	51.3	43.0	3.1	2.4	0.1
2010	92	4.00	49.6	45.7	2.6	1.8	0.2

Sponsor Reference No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (%)	NEUT (10^9/L)	LYMPH (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
2001	91	0.4	2.55	1.93	0.22	0.06	0.01
2002	91	0.5	2.18	3.92	0.19	0.10	0.00
2003	91	0.3	1.84	2.49	0.11	0.08	0.00
2004	91	0.2	2.19	3.29	0.16	0.13	0.01
2005	91	1.1	1.98	4.69	0.22	0.14	0.01
2006	92	0.6	2.09	2.58	0.15	0.08	0.01
2007	92	0.2	2.42	2.78	0.16	0.07	0.01
2008	92	0.1	0.97	1.50	0.05	0.10	0.00
2009	92	0.2	2.95	2.48	0.18	0.14	0.01
2010	92	0.2	1.98	1.83	0.10	0.07	0.01

Sponsor Reference No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (10^9/L)	RBC (10^12/L)	HGB (g/L)	HCT (L/L)	MCV (fL)	MCH (pg)
2001	91	0.02	8.23	143	0.439	53.4	17.4
2002	91	0.03	7.73	133	0.409	52.9	17.2
2003	91	0.01	7.35	134	0.395	53.7	18.2
2004	91	0.01	7.79	134	0.405	51.9	17.3
2005	91	0.08	7.72	137	0.425	55.0	17.8
2006	92	0.03	7.27	130	0.389	53.6	17.9
2007	92	0.01	7.86	134	0.412	52.5	17.0
2008	92	0.00	7.67	134	0.403	52.6	17.5
2009	92	0.01	7.76	133	0.406	52.3	17.1
2010	92	0.01	7.59	133	0.403	53.1	17.5

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Individual Hematology Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Hematology					
		MCHC (g/L)	RDWG (%)	PLT (10^9/L)	MPV (fL)	RETIC (10^9/L)	RETIC (%)
2001	91	326	12.6	775	8.4	249.0	3.0
2002	91	324	12.1	637	8.5	193.6	2.5
2003	91	339	12.1	648	8.5	172.3	2.3
2004	91	332	11.9	685	8.2	174.7	2.2
2005	91	323	12.5	767	7.4	205.5	2.7
2006	92	335	12.9	686	8.0	207.5	2.9
2007	92	325	12.9	612	8.8	166.8	2.1
2008	92	333	12.2	719	7.7	178.6	2.3
2009	92	327	12.5	872	7.3	174.8	2.3
2010	92	330	13.0	747	8.1	141.4	1.9

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Hematology			
		POLY	ROULEAUX	PLATELET CLUMPS	WBC MORPH
2001	91	-	-	-	-
2002	91	-	-	-	-
2003	91	-	-	-	-
2004	91	-	-	-	-
2005	91	-	-	-	-
2006	92	-	-	-	-
2007	92	-	-	-	-
2008	92	-	-	-	-
2009	92	-	-	-	-
2010	92	-	-	-	-

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Individual Hematology Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Hematology					
		WBC (10^9/L)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BASO (%)
3001	91	0.75	36.4	55.6	3.9	3.3	0.7
3002	91	3.28	37.3	58.4	2.3	1.7	0.2
3003	91	4.18	45.9	49.6	2.3	2.0	0.1
3004	91	5.15	35.6	60.2	2.4	1.5	0.1
3005	91	7.38	54.1	41.9	2.0	1.8	0.1
3006	92	3.02	22.8	71.3	3.5	1.9	0.2
3007	92	3.59	43.0	51.1	3.1	2.4	0.2
3008	92	4.46	47.6	50.0	1.1	1.0	0.2
3009	92	5.02	40.0	57.2	1.8	0.9	0.0
3010	92	5.29	37.2	58.2	3.2	1.0	0.3

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Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (%)	NEUT (10^9/L)	LYMPH (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
3001	91	0.1	0.27	0.42	0.03	0.02	0.01
3002	91	0.2	1.23	1.92	0.07	0.06	0.00
3003	91	0.2	1.92	2.07	0.10	0.08	0.00
3004	91	0.2	1.83	3.10	0.12	0.08	0.01
3005	91	0.1	4.00	3.09	0.15	0.13	0.01
3006	92	0.4	0.69	2.15	0.11	0.06	0.00
3007	92	0.2	1.55	1.83	0.11	0.09	0.01
3008	92	0.1	2.12	2.23	0.05	0.04	0.01
3009	92	0.2	2.01	2.87	0.09	0.04	0.00
3010	92	0.2	1.97	3.08	0.17	0.05	0.01

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (10^9/L)	RBC (10^12/L)	HGB (g/L)	HCT (L/L)	MCV (fL)	MCH (pg)
3001	91	0.00	6.55	121	0.378	57.7	18.5
3002	91	0.01	7.46	142	0.436	58.5	19.0
3003	91	0.01	7.80	136	0.415	53.2	17.4
3004	91	0.01	7.78	139	0.399	51.3	17.9
3005	91	0.01	7.52	138	0.406	54.0	18.4
3006	92	0.01	7.49	139	0.421	56.2	18.6
3007	92	0.01	7.67	127	0.382	49.9	16.5
3008	92	0.01	8.38	143	0.436	52.0	17.1
3009	92	0.01	7.58	142	0.422	55.7	18.7
3010	92	0.01	7.72	142	0.439	56.8	18.4

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Hematology					
		MCHC (g/L)	RDWG (%)	PLT (10^9/L)	MPV (fL)	RETIC (10^9/L)	RETIC (%)
3001	91	321	12.4	586	7.7	197.7	3.0
3002	91	325	11.3	769	8.2	170.6	2.3
3003	91	328	12.5	650	8.2	145.7	1.9
3004	91	349	11.4	522	8.4	169.0	2.2
3005	91	341	12.2	699	8.2	156.8	2.1
3006	92	331	12.5	592	8.2	222.4	3.0
3007	92	331	12.6	728	8.0	166.8	2.2
3008	92	328	12.7	686	7.7	185.3	2.2
3009	92	335	12.3	684	7.5	197.5	2.6
3010	92	324	12.0	796	7.7	182.1	2.4

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Hematology			
		POLY	ROULEAUX	PLATELET CLUMPS	WBC MORPH
3001	91	-	-	-	-
3002	91	-	-	-	-
3003	91	-	-	-	-
3004	91	-	-	-	-
3005	91	-	-	-	-
3006	92	-	-	-	-
3007	92	-	-	-	-
3008	92	-	-	-	-
3009	92	-	-	-	-
3010	92	-	-	-	-

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Hematology					
		WBC (10^9/L)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BASO (%)
4001	91	6.19	35.6	57.6	4.5	1.1	0.1
4002	91	5.11	29.2	63.5	3.3	3.5	0.2
4003	91	3.43	43.3	51.0	3.5	1.7	0.1
4004	91	5.69	32.4	60.4	3.6	2.6	0.2
4005	91	5.71	49.0	47.3	2.1	1.4	0.1
4006	92	3.34	31.1	60.1	5.3	2.6	0.3
4007	92	3.69	34.5	60.5	3.2	1.0	0.2
4008	92	4.72	36.0	60.5	2.3	1.0	0.1
4009	92	3.81	55.7	40.1	2.9	1.1	0.1
4010	92	2.55	32.1	62.9	3.0	1.4	0.4
4011	120	2.41	28.2	66.6	2.3	2.2	0.4
4012	120	3.52	53.1	43.6	1.6	1.3	0.1
4013	120	4.00	39.4	56.9	2.0	1.5	0.0
4014	120	4.95	50.4	46.0	2.3	1.1	0.1
4015	120	4.41	53.4	42.3	3.2	0.8	0.1

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (%)	NEUT (10^9/L)	LYMPH (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
4001	91	1.0	2.20	3.56	0.28	0.07	0.01
4002	91	0.3	1.49	3.24	0.17	0.18	0.01
4003	91	0.5	1.48	1.75	0.12	0.06	0.00
4004	91	0.8	1.84	3.44	0.21	0.15	0.01
4005	91	0.2	2.80	2.70	0.12	0.08	0.01
4006	92	0.6	1.04	2.01	0.18	0.09	0.01
4007	92	0.6	1.28	2.23	0.12	0.04	0.01
4008	92	0.1	1.70	2.86	0.11	0.05	0.00
4009	92	0.2	2.12	1.53	0.11	0.04	0.00
4010	92	0.2	0.82	1.60	0.08	0.04	0.01
4011	120	0.3	0.68	1.61	0.06	0.05	0.01
4012	120	0.2	1.87	1.53	0.06	0.05	0.00
4013	120	0.2	1.58	2.28	0.08	0.06	0.00
4014	120	0.2	2.50	2.28	0.11	0.05	0.00
4015	120	0.2	2.35	1.86	0.14	0.04	0.00

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Individual Hematology Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (10^9/L)	RBC (10^12/L)	HGB (g/L)	HCT (L/L)	MCV (fL)	MCH (pg)
4001	91	0.06	8.04	142	0.416	51.7	17.6
4002	91	0.02	8.42	147	0.456	54.1	17.5
4003	91	0.02	7.18	126	0.375	52.2	17.5
4004	91	0.05	8.24	144	0.437	53.0	17.4
4005	91	0.01	7.58	137	0.422	55.6	18.0
4006	92	0.02	7.89	136	0.417	52.8	17.2
4007	92	0.02	7.69	138	0.406	52.8	17.9
4008	92	0.00	7.74	131	0.407	52.6	16.9
4009	92	0.01	7.79	136	0.413	53.0	17.5
4010	92	0.01	7.66	123	0.377	49.2	16.0
4011	120	0.01	7.46	134	0.395	52.9	18.0
4012	120	0.01	7.82	136	0.414	53.0	17.4
4013	120	0.01	7.30	128	0.375	51.4	17.6
4014	120	0.01	7.73	137	0.427	55.2	17.8
4015	120	0.01	7.45	130	0.394	52.9	17.4

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Individual Hematology Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Hematology					
		MCHC (g/L)	RDWG (%)	PLT (10^9/L)	MPV (fL)	RETIC (10^9/L)	RETIC (%)
4001	91	341	12.5	647	8.4	159.0	2.0
4002	91	324	12.6	695	7.9	216.6	2.6
4003	91	336	12.0	533	8.5	168.7	2.3
4004	91	328	11.6	693	8.1	177.5	2.2
4005	91	324	11.7	546	9.4	184.7	2.4
4006	92	326	12.2	696	7.6	215.1	2.7
4007	92	339	12.7	684	7.9	199.6	2.6
4008	92	322	12.7	773	7.8	189.6	2.5
4009	92	330	12.2	645	7.9	172.2	2.2
4010	92	326	13.0	540	8.7	190.7	2.5
4011	120	340	12.5	658	9.3	185.1	2.5
4012	120	329	11.9	582	9.4	175.7	2.2
4013	120	342	12.5	636	9.2	193.6	2.7
4014	120	322	12.7	897	8.7	201.7	2.6
4015	120	330	12.9	667	9.1	168.1	2.3

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Individual Hematology Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Hematology			
		POLY	ROULEAUX	PLATELET CLUMPS	WBC MORPH
4001	91	-	-	-	-
4002	91	-	-	-	-
4003	91	-	-	-	-
4004	91	-	-	-	-
4005	91	-	-	-	-
4006	92	-	-	-	-
4007	92	-	-	-	-
4008	92	-	-	-	-
4009	92	-	-	-	-
4010	92	-	-	-	-
4011	120	-	-	-	-
4012	120	-	-	-	-
4013	120	-	-	-	-
4014	120	-	-	-	-
4015	120	-	-	-	-

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Hematology					
		WBC (10^9/L)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BASO (%)
1501	91	2.12	31.8	65.5	1.5	1.0	0.2
1502	91	3.18	29.3	66.2	2.7	1.2	0.1
1503	91	4.07	43.4	51.4	3.2	1.7	0.0
1504	91	5.59	25.5	70.8	2.2	1.1	0.1
1505	91	4.67	29.4	66.4	2.2	1.1	0.0
1506	92	2.90	37.9	57.9	2.3	1.3	0.2
1507	92	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT
1508	92	4.21	23.1	72.2	2.3	2.2	0.1
1509	92	3.43	42.9	51.8	3.9	1.2	0.0
1510	92	2.23	35.4	59.4	3.5	1.3	0.1
1511	120	3.43	40.9	55.0	2.0	1.7	0.1
1512	120	3.08	30.6	64.8	2.9	1.4	0.1
1513	120	3.37	36.3	58.9	2.7	1.6	0.3
1514	120	6.10	36.2	58.6	3.3	1.4	0.2
1515	120	3.22	30.5	63.0	4.7	0.6	0.2

Sponsor Reference No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (%)	NEUT (10^9/L)	LYMPH (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
1501	91	0.1	0.67	1.39	0.03	0.02	0.00
1502	91	0.5	0.93	2.10	0.09	0.04	0.00
1503	91	0.3	1.77	2.09	0.13	0.07	0.00
1504	91	0.3	1.43	3.96	0.12	0.06	0.00
1505	91	1.0	1.37	3.10	0.10	0.05	0.00
1506	92	0.3	1.10	1.68	0.07	0.04	0.01
1507	92	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT
1508	92	0.2	0.97	3.04	0.10	0.09	0.00
1509	92	0.2	1.47	1.77	0.13	0.04	0.00
1510	92	0.3	0.79	1.32	0.08	0.03	0.00
1511	120	0.2	1.40	1.89	0.07	0.06	0.00
1512	120	0.2	0.94	2.00	0.09	0.04	0.00
1513	120	0.1	1.22	1.99	0.09	0.05	0.01
1514	120	0.4	2.21	3.57	0.20	0.09	0.01
1515	120	1.1	0.98	2.03	0.15	0.02	0.00

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Individual Hematology Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (10^9/L)	RBC (10^12/L)	HGB (g/L)	HCT (L/L)	MCV (fL)	MCH (pg)
1501	91	0.00	5.87	111	0.328	55.8	18.8
1502	91	0.02	6.33	117	0.350	55.3	18.5
1503	91	0.01	6.24	113	0.347	55.7	18.1
1504	91	0.02	7.00	128	0.388	55.5	18.2
1505	91	0.05	6.72	129	0.378	56.3	19.2
1506	92	0.01	6.71	132	0.384	57.3	19.8
1507	92	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT
1508	92	0.01	7.39	133	0.405	54.9	17.9
1509	92	0.01	6.46	121	0.365	56.5	18.7
1510	92	0.01	6.56	124	0.374	56.9	18.8
1511	120	0.01	6.51	123	0.361	55.4	18.8
1512	120	0.01	6.64	120	0.363	54.7	18.1
1513	120	0.00	6.85	119	0.350	51.1	17.4
1514	120	0.02	6.90	130	0.385	55.8	18.8
1515	120	0.03	7.11	126	0.384	54.0	17.8

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Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Hematology					
		MCHC (g/L)	RDWG (%)	PLT (10^9/L)	MPV (fL)	RETIC (10^9/L)	RETIC (%)
1501	91	338	11.5	718	8.6	165.0	2.8
1502	91	335	11.1	771	8.6	189.7	3.0
1503	91	324	11.8	753	8.4	231.4	3.7
1504	91	328	11.5	759	8.1	177.3	2.5
1505	91	341	11.0	713	8.8	161.9	2.4
1506	92	345	11.2	803	7.9	160.4	2.4
1507	92	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT
1508	92	327	12.0	816	7.4	232.7	3.1
1509	92	332	12.4	759	8.2	170.5	2.6
1510	92	331	11.5	764	7.4	148.6	2.3
1511	120	340	10.6	712	9.4	153.7	2.4
1512	120	331	11.1	737	8.5	157.4	2.4
1513	120	340	11.6	796	9.0	142.4	2.1
1514	120	337	10.8	UTDM	8.8	178.7	2.6
1515	120	329	10.9	751	8.6	166.5	2.3

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Individual Hematology Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Hematology			
		POLY	ROULEAUX	PLATELET CLUMPS	WBC MORPH
1501	91	-	-	-	-
1502	91	-	-	-	-
1503	91	-	-	-	-
1504	91	-	-	-	-
1505	91	-	-	-	-
1506	92	-	-	-	-
1507	92	-	-	-	-
1508	92	-	-	-	-
1509	92	-	-	-	-
1510	92	-	-	-	-
1511	120	-	-	-	-
1512	120	-	-	-	-
1513	120	-	-	-	-
1514	120	1+	1+	4+	NAF
1515	120	-	-	-	-

Sponsor Reference No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Hematology					
		WBC (10^9/L)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BASO (%)
2501	91	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT
2502	91	3.30	31.2	64.7	2.6	1.0	0.0
2503	91	3.83	36.9	58.8	2.9	1.2	0.0
2504	91	5.39	35.7	59.8	2.7	1.5	0.0
2505	91	1.96	30.0	63.0	4.2	2.2	0.1
2506	92	2.28	35.5	60.6	2.0	1.6	0.2
2507	92	2.90	45.7	49.4	3.4	1.1	0.1
2508	92	3.65	29.9	66.1	2.3	1.3	0.1
2509	92	3.73	30.7	65.9	1.8	0.9	0.2
2510	92	3.12	55.9	39.6	2.7	1.0	0.3

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Individual Hematology Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (%)	NEUT (10^9/L)	LYMPH (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
2501	91	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT
2502	91	0.4	1.03	2.14	0.09	0.03	0.00
2503	91	0.1	1.41	2.25	0.11	0.05	0.00
2504	91	0.2	1.93	3.23	0.15	0.08	0.00
2505	91	0.5	0.59	1.24	0.08	0.04	0.00
2506	92	0.3	0.81	1.38	0.05	0.04	0.00
2507	92	0.2	1.33	1.43	0.10	0.03	0.00
2508	92	0.3	1.09	2.41	0.08	0.05	0.00
2509	92	0.5	1.14	2.46	0.07	0.03	0.01
2510	92	0.4	1.74	1.24	0.08	0.03	0.01

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Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (10^9/L)	RBC (10^12/L)	HGB (g/L)	HCT (L/L)	MCV (fL)	MCH (pg)
2501	91	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT
2502	91	0.01	6.58	124	0.374	56.8	18.9
2503	91	0.00	6.65	117	0.353	53.0	17.6
2504	91	0.01	6.88	120	0.359	52.2	17.4
2505	91	0.01	6.01	106	0.314	52.2	17.7
2506	92	0.01	6.63	126	0.381	57.5	19.1
2507	92	0.01	6.42	119	0.359	56.0	18.6
2508	92	0.01	7.15	127	0.388	54.3	17.8
2509	92	0.02	6.92	120	0.367	53.1	17.4
2510	92	0.01	6.56	113	0.345	52.5	17.2

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Individual Hematology Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Hematology					
		MCHC (g/L)	RDWG (%)	PLT (10^9/L)	MPV (fL)	RETIC (10^9/L)	RETIC (%)
2501	91	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT
2502	91	332	10.5	675	8.7	178.0	2.7
2503	91	331	11.4	960	8.4	168.6	2.5
2504	91	334	11.9	564	9.4	201.7	2.9
2505	91	339	11.6	565	8.2	181.1	3.0
2506	92	332	11.3	706	8.2	208.6	3.1
2507	92	332	11.1	681	8.1	201.0	3.1
2508	92	328	11.7	675	7.9	199.7	2.8
2509	92	327	11.4	613	8.0	156.8	2.3
2510	92	327	11.8	780	7.5	185.7	2.8

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Individual Hematology Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Hematology			
		POLY	ROULEAUX	PLATELET CLUMPS	WBC MORPH
2501	91	-	-	-	-
2502	91	-	-	-	-
2503	91	-	-	-	-
2504	91	-	-	-	-
2505	91	-	-	-	-
2506	92	-	-	-	-
2507	92	-	-	-	-
2508	92	-	-	-	-
2509	92	-	-	-	-
2510	92	-	-	-	-

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Individual Hematology Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Hematology					
		WBC (10^9/L)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BASO (%)
3501	91	1.27	29.5	67.5	1.8	0.6	0.2
3502	91	4.76	29.1	65.9	3.5	1.1	0.1
3503	91	3.34	50.2	44.6	3.1	1.8	0.1
3504	91	5.02	24.4	70.7	3.1	1.4	0.1
3505	91	5.25	44.6	51.9	2.4	0.8	0.1
3506	92	2.64	33.3	60.7	3.8	1.6	0.2
3507	92	2.40	42.6	51.5	3.9	1.8	0.1
3508	92	3.26	29.4	65.9	2.9	1.3	0.0
3509	92	3.88	41.4	54.1	2.9	1.1	0.1
3510	92	4.06	31.6	64.3	2.0	1.4	0.1

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (%)	NEUT (10^9/L)	LYMPH (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
3501	91	0.4	0.37	0.85	0.02	0.01	0.00
3502	91	0.3	1.39	3.14	0.17	0.05	0.00
3503	91	0.1	1.68	1.49	0.10	0.06	0.00
3504	91	0.3	1.23	3.55	0.16	0.07	0.00
3505	91	0.2	2.34	2.73	0.12	0.04	0.00
3506	92	0.3	0.88	1.60	0.10	0.04	0.01
3507	92	0.1	1.02	1.23	0.09	0.04	0.00
3508	92	0.4	0.96	2.15	0.09	0.04	0.00
3509	92	0.3	1.61	2.10	0.11	0.04	0.00
3510	92	0.5	1.28	2.62	0.08	0.06	0.00

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (10^9/L)	RBC (10^12/L)	HGB (g/L)	HCT (L/L)	MCV (fL)	MCH (pg)
3501	91	0.00	5.82	108	0.331	57.0	18.6
3502	91	0.02	7.26	130	0.386	53.1	17.9
3503	91	0.00	5.96	120	0.356	59.6	20.2
3504	91	0.02	7.54	134	0.411	54.6	17.8
3505	91	0.01	6.38	126	0.360	56.4	19.7
3506	92	0.01	6.55	128	0.378	57.7	19.5
3507	92	0.00	6.61	115	0.357	54.0	17.4
3508	92	0.01	7.39	136	0.419	56.7	18.4
3509	92	0.01	6.71	122	0.368	54.8	18.2
3510	92	0.02	7.49	130	0.404	54.0	17.4

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Hematology					
		MCHC (g/L)	RDWG (%)	PLT (10^9/L)	MPV (fL)	RETIC (10^9/L)	RETIC (%)
3501	91	326	10.9	568	8.2	162.3	2.8
3502	91	338	11.1	695	8.1	188.9	2.6
3503	91	338	11.1	616	9.4	164.0	2.8
3504	91	326	11.0	603	9.4	174.3	2.3
3505	91	350	10.5	557	9.0	159.6	2.5
3506	92	339	11.4	820	7.7	172.0	2.6
3507	92	323	11.6	753	7.6	194.6	2.9
3508	92	324	11.8	637	7.7	222.5	3.0
3509	92	332	11.8	603	7.8	170.3	2.5
3510	92	322	11.7	836	7.4	236.3	3.2

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Hematology			
		POLY	ROULEAUX	PLATELET CLUMPS	WBC MORPH
3501	91	-	-	-	-
3502	91	-	-	-	-
3503	91	-	-	-	-
3504	91	-	-	-	-
3505	91	-	-	-	-
3506	92	-	-	-	-
3507	92	-	-	-	-
3508	92	-	-	-	-
3509	92	-	-	-	-
3510	92	-	-	-	-

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Hematology					
		WBC (10^9/L)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BASO (%)
4501	91	4.61	27.5	68.8	2.4	0.9	0.1
4502	91	4.06	22.1	72.8	3.3	1.0	0.1
4503	91	4.56	14.3	82.4	2.0	0.7	0.2
4504	91	4.88	25.3	71.9	1.7	0.7	0.3
4505	91	3.12	25.9	68.8	2.8	1.4	0.1
4506	92	3.58	29.7	65.0	4.0	0.8	0.1
4507	92	4.43	18.7	77.2	2.4	1.1	0.1
4508	92	5.37	32.8	62.7	2.7	1.3	0.2
4509	92	4.66	29.1	66.9	2.6	0.8	0.1
4510	92	3.63	27.8	65.9	4.6	1.0	0.0
4511	120	1.55	30.4	65.2	3.2	1.2	0.0
4512	120	3.93	71.2	26.1	2.0	0.5	0.1
4513	120	4.27	29.0	67.2	2.6	0.8	0.2
4514	120	4.19	38.6	55.7	3.4	0.9	0.1
4515	120	5.27	32.3	63.2	2.8	1.0	0.1

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (%)	NEUT (10^9/L)	LYMPH (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
4501	91	0.3	1.27	3.18	0.11	0.04	0.00
4502	91	0.6	0.90	2.96	0.14	0.04	0.00
4503	91	0.5	0.65	3.76	0.09	0.03	0.01
4504	91	0.1	1.24	3.51	0.08	0.03	0.01
4505	91	0.9	0.81	2.14	0.09	0.04	0.00
4506	92	0.3	1.06	2.33	0.14	0.03	0.00
4507	92	0.4	0.83	3.42	0.11	0.05	0.01
4508	92	0.3	1.76	3.37	0.15	0.07	0.01
4509	92	0.6	1.36	3.12	0.12	0.04	0.00
4510	92	0.6	1.01	2.39	0.17	0.03	0.00
4511	120	0.1	0.47	1.01	0.05	0.02	0.00
4512	120	0.1	2.80	1.03	0.08	0.02	0.00
4513	120	0.3	1.24	2.87	0.11	0.03	0.01
4514	120	1.3	1.61	2.33	0.14	0.04	0.00
4515	120	0.6	1.70	3.33	0.15	0.05	0.00

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Hematology					
		LUC (10^9/L)	RBC (10^12/L)	HGB (g/L)	HCT (L/L)	MCV (fL)	MCH (pg)
4501	91	0.01	6.58	123	0.373	56.7	18.7
4502	91	0.02	6.38	118	0.348	54.6	18.4
4503	91	0.02	6.48	114	0.338	52.1	17.6
4504	91	0.01	6.95	126	0.379	54.6	18.1
4505	91	0.03	7.11	130	0.395	55.6	18.3
4506	92	0.01	7.01	128	0.383	54.6	18.3
4507	92	0.02	7.06	124	0.371	52.6	17.5
4508	92	0.01	7.65	131	0.397	51.8	17.1
4509	92	0.03	7.17	128	0.386	53.9	17.8
4510	92	0.02	6.69	127	0.380	56.8	19.0
4511	120	0.00	6.34	118	0.358	56.5	18.6
4512	120	0.00	6.23	117	0.340	54.6	18.7
4513	120	0.01	6.33	123	0.367	58.0	19.5
4514	120	0.05	6.89	124	0.370	53.7	18.0
4515	120	0.03	6.98	124	0.365	52.3	17.8

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Hematology					
		MCHC (g/L)	RDWG (%)	PLT (10^9/L)	MPV (fL)	RETIC (10^9/L)	RETIC (%)
4501	91	329	11.1	593	8.0	189.4	2.9
4502	91	338	11.0	686	8.3	195.0	3.1
4503	91	337	11.8	690	8.2	196.4	3.0
4504	91	332	10.5	619	8.4	170.5	2.5
4505	91	328	10.6	824	8.5	169.2	2.4
4506	92	335	11.3	844	7.8	158.4	2.3
4507	92	333	12.0	676	7.6	258.2	3.7
4508	92	330	11.0	870	7.4	180.8	2.4
4509	92	331	11.5	713	7.4	218.5	3.0
4510	92	334	11.4	697	7.8	163.3	2.4
4511	120	330	11.3	670	8.6	199.2	3.1
4512	120	343	11.2	771	8.9	202.4	3.3
4513	120	336	11.4	591	8.7	157.9	2.5
4514	120	336	10.9	691	8.4	117.2	1.7
4515	120	341	11.5	609	8.9	187.5	2.7

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Hematology Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Hematology			
		POLY	ROULEAUX	PLATELET CLUMPS	WBC MORPH
4501	91	-	-	-	-
4502	91	-	-	-	-
4503	91	-	-	-	-
4504	91	-	-	-	-
4505	91	-	-	-	-
4506	92	-	-	-	-
4507	92	-	-	-	-
4508	92	-	-	-	-
4509	92	-	-	-	-
4510	92	-	-	-	-
4511	120	-	-	-	-
4512	120	-	-	-	-
4513	120	-	-	-	-
4514	120	-	-	-	-
4515	120	-	-	-	-

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 19

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Individual Coagulation Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Coagulation		
		PT (sec)	APTT (sec)	FIB (g/L)
1001	91	21.0	15.7	2.52
1002	91	21.2	16.9	2.60
1003	91	21.6	16.8	2.35
1004	91	18.3	12.2	2.74
1005	91	20.4	14.9	2.92
1006	92	17.8	12.4	2.49
1007	92	19.7	16.0	2.31
1008	92	18.2	14.0	2.64
1009	92	CLOT	CLOT	CLOT
1010	92	19.3	14.7	2.64
1011	120	17.9	16.8	2.87
1012	120	16.6	16.9	2.65
1013	120	21.2	17.2	2.39
1014	120	19.3	17.5	2.57
1015	120	18.9	17.6	2.39

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 19

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Individual Coagulation Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Coagulation		
		PT (sec)	APTT (sec)	FIB (g/L)
2001	91	18.7	12.2	2.34
2002	91	21.1	15.9	2.66
2003	91	23.4	15.4	2.57
2004	91	22.0	15.2	2.36
2005	91	22.1	16.7	2.87
2006	92	20.9	15.3	4.74
2007	92	20.2	14.5	2.58
2008	92	20.5	16.0	2.46
2009	92	19.1	13.8	2.64
2010	92	19.8	13.5	2.42

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Coagulation Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Coagulation		
		PT (sec)	APTT (sec)	FIB (g/L)
3001	91	21.4	15.9	2.97
3002	91	20.3	12.1	2.67
3003	91	CLOT	CLOT	CLOT
3004	91	20.7	14.4	2.52
3005	91	CLOT	CLOT	CLOT
3006	92	18.7	17.3	2.62
3007	92	19.8	12.7	2.36
3008	92	20.5	15.3	2.56
3009	92	21.9	15.6	2.56
3010	92	20.5	14.1	2.70

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Coagulation Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Coagulation		
		PT (sec)	APTT (sec)	FIB (g/L)
4001	91	21.1	11.3	2.59
4002	91	21.4	13.7	2.76
4003	91	19.7	12.4	2.55
4004	91	22.8	15.3	2.55
4005	91	CLOT	CLOT	CLOT
4006	92	21.4	15.6	2.57
4007	92	21.4	15.9	2.48
4008	92	22.4	15.9	2.89
4009	92	21.5	16.1	2.69
4010	92	22.5	20.2	2.39
4011	120	19.2	17.3	2.68
4012	120	19.8	16.5	2.21
4013	120	18.4	16.6	2.41
4014	120	19.2	17.8	2.38
4015	120	18.3	15.8	2.08

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Coagulation Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Coagulation		
		PT (sec)	APTT (sec)	FIB (g/L)
1501	91	21.1	16.7	1.70
1502	91	20.2	17.7	1.51
1503	91	21.9	16.1	2.03
1504	91	21.4	16.2	1.78
1505	91	21.6	16.1	1.98
1506	92	20.0	15.2	1.70
1507	92	19.6	17.7	1.85
1508	92	19.5	16.4	2.48
1509	92	20.3	17.1	1.70
1510	92	19.6	15.3	1.88
1511	120	20.2	18.2	1.87
1512	120	20.5	17.1	1.64
1513	120	19.9	16.8	1.64
1514	120	20.9	17.0	1.82
1515	120	19.9	16.7	1.72

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 19

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Individual Coagulation Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Coagulation		
		PT (sec)	APTT (sec)	FIB (g/L)
2501	91	21.2	16.7	1.86
2502	91	21.2	15.0	1.70
2503	91	21.5	15.1	1.84
2504	91	19.6	13.4	2.32
2505	91	19.9	15.9	1.87
2506	92	20.0	17.4	1.92
2507	92	19.7	15.7	1.77
2508	92	20.3	16.2	1.95
2509	92	19.7	16.6	2.05
2510	92	19.1	12.8	1.96

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 19

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Individual Coagulation Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Coagulation		
		PT (sec)	APTT (sec)	FIB (g/L)
3501	91	21.5	17.5	2.09
3502	91	CLOT	CLOT	CLOT
3503	91	20.4	14.4	1.64
3504	91	21.5	16.0	2.10
3505	91	20.4	15.0	1.75
3506	92	19.8	14.4	1.61
3507	92	18.4	11.6	1.80
3508	92	19.5	12.4	2.32
3509	92	15.8	12.3	1.68
3510	92	20.0	15.2	2.00

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Coagulation Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Coagulation		
		PT (sec)	APTT (sec)	FIB (g/L)
4501	91	21.6	13.2	1.58
4502	91	18.8	11.6	1.66
4503	91	22.5	16.6	1.55
4504	91	CLOT	CLOT	CLOT
4505	91	21.2	12.9	2.13
4506	92	20.3	15.1	2.57
4507	92	20.7	16.9	2.66
4508	92	20.7	16.1	1.86
4509	92	18.0	11.6	1.85
4510	92	20.6	15.7	1.77
4511	120	19.5	17.1	1.82
4512	120	20.7	16.6	1.77
4513	120	21.3	17.5	1.87
4514	120	19.7	16.1	1.65
4515	120	19.5	17.1	2.14

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Appendix 20

16-Mar-2023 09:59:30

Individual Clinical Chemistry Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Biochemistry					
		AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	TBIL (umol/L)	BILEAC (umol/L)
1001	91	88	26	77	2 [a]	2.7	9.1
1002	91	90	24	68	2 [a]	2.6	28.0
1003	91	111	33	62	2 [a]	2.6	7.2
1004	91	81	38	61	2 [a]	2.7	21.1
1005	91	76	20	57	2 [a]	2.7	8.7
1006	92	84	23	39	2 [a]	2.9	26.7
1007	92	89	35	68	2 [a]	2.8	10.5
1008	92	73	22	53	2 [a]	2.9	11.5
1009	92	78	26	58	2 [a]	3.2	29.4
1010	92	91	31	45	2 [a]	3.7	7.4
1011	120	87	24	36	2 [a]	2.5	29.6
1012	120	70	30	42	2 [a]	2.8	50.9
1013	120	88	26	53	2 [a]	3.0	28.9
1014	120	99	42	42	2 [a]	3.1	28.5
1015	120	76	21	50	2 [a]	2.5	19.0

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 20

16-Mar-2023 09:59:30

Individual Clinical Chemistry Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Biochemistry					
		UREA (mmol/L)	CREAT (umol/L)	GLUC (mmol/L)	CHOL (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
1001	91	7.4	48	8.07	1.97	0.42	0.36 [a]
1002	91	7.4	43	8.68	0.96	0.26	0.36 [a]
1003	91	9.1	47	7.18	1.61	0.37	0.36 [a]
1004	91	7.5	42	9.52	2.08	0.48	0.36 [a]
1005	91	6.9	43	11.37	1.55	0.41	0.36 [a]
1006	92	8.1	51	9.76	1.73	0.48	0.36 [a]
1007	92	6.7	47	8.88	2.54	0.66	0.36 [a]
1008	92	7.5	49	7.98	1.55	0.45	0.36 [a]
1009	92	6.7	39	8.06	2.20	0.59	0.36 [a]
1010	92	8.1	42	9.20	1.34	0.45	0.36 [a]
1011	120	7.9	52	11.26	1.67	0.45	0.36 [a]
1012	120	7.3	48	7.90	1.84	0.53	0.36 [a]
1013	120	6.2	42	7.55	1.08	0.34	0.36 [a]
1014	120	6.9	42	9.15	1.54	0.42	0.36 [a]
1015	120	8.2	43	7.38	2.37	0.58	0.36 [a]

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 20

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Biochemistry					
		TRIG (mmol/L)	TPROT (g/L)	ALB (g/L)	GLOB (g/L)	A/G (ratio)	CA (mmol/L)
1001	91	1.25	60.8	32.2	28.6	1.1	2.52
1002	91	0.76	54.3	30.7	23.6	1.3	2.48
1003	91	0.85	57.0	31.8	25.2	1.3	2.53
1004	91	0.84	58.8	31.9	26.9	1.2	2.56
1005	91	0.89	57.7	31.7	26.0	1.2	2.62
1006	92	0.58	55.7	31.4	24.3	1.3	2.48
1007	92	3.29	59.0	33.5	25.5	1.3	2.48
1008	92	0.68	57.4	31.6	25.8	1.2	2.53
1009	92	1.11	58.5	32.6	25.9	1.3	2.65
1010	92	1.24	62.9	34.6	28.3	1.2	2.63
1011	120	0.63	56.0	30.5	25.5	1.2	2.40
1012	120	0.72	59.3	32.1	27.2	1.2	2.46
1013	120	0.44	53.2	30.8	22.4	1.4	2.50
1014	120	0.67	56.3	31.5	24.8	1.3	2.56
1015	120	0.46	57.4	31.7	25.7	1.2	2.63

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 20

16-Mar-2023 09:59:30

Individual Clinical Chemistry Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Biochemistry			
		NA (mmol/L)	K (mmol/L)	CL (mmol/L)	PHOS (mmol/L)
1001	91	142	4.3	103	2.18
1002	91	140	4.1	102	2.47
1003	91	140	4.2	102	2.62
1004	91	140	3.9	102	2.43
1005	91	140	4.2	103	2.05
1006	92	142	3.7	105	1.89
1007	92	142	3.9	102	1.84
1008	92	142	4.1	103	2.35
1009	92	142	4.2	104	2.41
1010	92	142	4.4	105	2.28
1011	120	141	4.1	103	1.74
1012	120	141	3.7	102	1.97
1013	120	140	4.6	104	2.58
1014	120	143	4.3	105	2.27
1015	120	143	4.5	106	2.30

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 20

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Biochemistry					
		AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	TBIL (umol/L)	BILEAC (umol/L)
2001	91	101	28	66	2 [a]	2.4	17.6
2002	91	83	29	54	2 [a]	2.5	16.9
2003	91	100	25	63	2 [a]	2.7	28.1
2004	91	93	24	57	2 [a]	2.8	7.8
2005	91	75	30	58	2 [a]	3.1	35.6
2006	92	92	24	88	2 [a]	3.4	12.1
2007	92	150	104	83	2 [a]	2.6	8.5
2008	92	66	19	43	2 [a]	2.4	12.4
2009	92	80	24	53	2 [a]	2.4	33.7
2010	92	103	31	61	2 [a]	2.8	8.1

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 20

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Biochemistry					
		UREA (mmol/L)	CREAT (umol/L)	GLUC (mmol/L)	CHOL (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
2001	91	7.0	43	7.17	1.27	0.33	0.36 [a]
2002	91	9.4	50	10.03	1.41	0.40	0.36 [a]
2003	91	5.8	41	7.82	1.09	0.29	0.36 [a]
2004	91	7.5	43	7.86	1.65	0.43	0.36 [a]
2005	91	5.9	41	10.19	2.24	0.58	0.36 [a]
2006	92	7.3	43	8.17	2.39	0.68	0.36 [a]
2007	92	5.7	45	9.00	1.53	0.54	0.36 [a]
2008	92	6.1	46	10.17	1.93	0.57	0.36 [a]
2009	92	7.1	39	7.93	1.75	0.52	0.36 [a]
2010	92	7.0	43	7.72	1.83	0.57	0.36 [a]

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Biochemistry					
		TRIG (mmol/L)	TPROT (g/L)	ALB (g/L)	GLOB (g/L)	A/G (ratio)	CA (mmol/L)
2001	91	1.26	53.6	29.6	24.0	1.2	2.48
2002	91	1.05	57.5	32.1	25.4	1.3	2.57
2003	91	0.75	53.3	29.7	23.6	1.3	2.53
2004	91	1.18	56.4	31.6	24.8	1.3	2.63
2005	91	0.98	63.2	33.4	29.8	1.1	2.69
2006	92	1.19	56.3	30.7	25.6	1.2	2.66
2007	92	1.56	61.0	34.5	26.5	1.3	2.54
2008	92	0.71	57.9	31.8	26.1	1.2	2.52
2009	92	0.79	55.3	30.9	24.4	1.3	2.55
2010	92	0.54	58.4	32.9	25.5	1.3	2.50

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Biochemistry			
		NA (mmol/L)	K (mmol/L)	CL (mmol/L)	PHOS (mmol/L)
2001	91	141	4.3	103	1.93
2002	91	139	4.5	101	1.86
2003	91	140	4.5	103	2.56
2004	91	141	4.5	102	2.70
2005	91	140	4.5	100	2.40
2006	92	143	4.5	103	2.06
2007	92	144	4.1	106	1.72
2008	92	140	4.2	103	1.88
2009	92	141	4.2	103	2.59
2010	92	142	4.2	103	1.96

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Biochemistry					
		AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	TBIL (umol/L)	BILEAC (umol/L)
3001	91	74	34	73	2 [a]	2.1	13.8
3002	91	92	29	62	2 [a]	2.7	14.7
3003	91	131	46	53	2 [a]	2.6	13.4
3004	91	92	32	51	2 [a]	2.3	23.3
3005	91	77	25	71	2 [a]	2.5	6.8
3006	92	87	19	44	2 [a]	2.8	7.5
3007	92	89	28	73	2 [a]	2.8	10.8
3008	92	109	49	55	2 [a]	2.4	8.4
3009	92	89	32	56	2 [a]	3.1	7.4
3010	92	72	23	48	2 [a]	3.0	54.9

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Biochemistry					
		UREA (mmol/L)	CREAT (umol/L)	GLUC (mmol/L)	CHOL (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
3001	91	6.9	47	11.57	1.95	0.53	0.36 [a]
3002	91	7.5	48	7.54	1.88	0.46	0.36 [a]
3003	91	7.1	41	7.25	1.52	0.41	0.36 [a]
3004	91	7.2	39	6.91	1.90	0.45	0.36 [a]
3005	91	5.1	40	7.30	2.06	0.48	0.36 [a]
3006	92	6.6	40	13.12	1.69	0.53	0.36 [a]
3007	92	6.1	39	9.75	1.67	0.50	0.36 [a]
3008	92	6.7	43	8.10	1.44	0.43	0.36 [a]
3009	92	6.3	40	10.40	1.90	0.61	0.36 [a]
3010	92	6.9	40	12.06	1.56	0.48	0.36 [a]

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Biochemistry					
		TRIG (mmol/L)	TPROT (g/L)	ALB (g/L)	GLOB (g/L)	A/G (ratio)	CA (mmol/L)
3001	91	1.25	57.2	31.9	25.3	1.3	2.54
3002	91	0.99	56.1	31.0	25.1	1.2	2.56
3003	91	1.08	56.8	31.8	25.0	1.3	2.56
3004	91	0.57	52.8	29.9	22.9	1.3	2.54
3005	91	0.92	59.1	33.1	26.0	1.3	2.60
3006	92	1.24	61.8	33.7	28.1	1.2	2.56
3007	92	0.98	55.3	31.3	24.0	1.3	2.46
3008	92	1.16	54.1	30.8	23.3	1.3	2.57
3009	92	1.06	60.7	34.2	26.5	1.3	2.57
3010	92	1.30	60.1	33.8	26.3	1.3	2.62

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Biochemistry			
		NA (mmol/L)	K (mmol/L)	CL (mmol/L)	PHOS (mmol/L)
3001	91	142	3.7	101	1.63
3002	91	142	4.1	103	1.49
3003	91	142	4.5	104	2.82
3004	91	140	4.5	102	2.43
3005	91	141	4.3	103	2.23
3006	92	139	4.6	104	1.88
3007	92	138	4.1	102	1.59
3008	92	144	4.2	106	2.48
3009	92	141	4.4	103	2.23
3010	92	143	4.7	104	2.46

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Biochemistry					
		AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	TBIL (umol/L)	BILEAC (umol/L)
4001	91	93	31	54	2 [a]	2.6	7.9
4002	91	102	50	61	2 [a]	2.7	9.3
4003	91	81	26	63	2 [a]	2.6	49.2
4004	91	87	26	64	2 [a]	3.4	10.9
4005	91	101	26	49	2 [a]	2.8	9.5
4006	92	130	39	55	2 [a]	2.4	8.2
4007	92	83	26	66	2 [a]	2.1	10.4
4008	92	103	31	78	2 [a]	2.6	7.6
4009	92	102	31	59	2 [a]	2.8	5.8
4010	92	86	26	49	2 [a]	2.1	10.0
4011	120	111	51	60	2 [a]	2.8	12.8
4012	120	81	25	48	2 [a]	2.4	11.6
4013	120	89	21	36	2 [a]	2.3	26.4
4014	120	74	19	45	2 [a]	2.7	31.1
4015	120	88	28	57	2 [a]	2.4	7.1

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Biochemistry					
		UREA (mmol/L)	CREAT (umol/L)	GLUC (mmol/L)	CHOL (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
4001	91	6.7	44	12.04	1.41	0.40	0.36 [a]
4002	91	8.0	43	10.15	1.91	0.54	0.36 [a]
4003	91	7.7	40	8.21	1.56	0.41	0.36 [a]
4004	91	5.7	44	10.85	1.48	0.43	0.36 [a]
4005	91	5.4	39	8.52	1.61	0.44	0.36 [a]
4006	92	8.4	43	12.04	1.49	0.48	0.36 [a]
4007	92	6.7	40	9.41	1.50	0.45	0.36 [a]
4008	92	6.5	41	9.24	1.54	0.48	0.36 [a]
4009	92	5.5	38	7.82	1.54	0.50	0.36 [a]
4010	92	7.1	36	8.27	1.30	0.44	0.36 [a]
4011	120	6.5	44	9.24	1.67	0.48	0.36 [a]
4012	120	7.9	48	9.87	1.48	0.39	0.36 [a]
4013	120	8.9	44	7.78	1.72	0.47	0.36 [a]
4014	120	6.9	37	8.51	1.58	0.43	0.36 [a]
4015	120	7.3	40	7.58	1.65	0.44	0.36 [a]

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Biochemistry					
		TRIG (mmol/L)	TPROT (g/L)	ALB (g/L)	GLOB (g/L)	A/G (ratio)	CA (mmol/L)
4001	91	1.06	60.5	31.6	28.9	1.1	2.46
4002	91	1.14	65.1	34.2	30.9	1.1	2.52
4003	91	0.94	54.9	29.8	25.1	1.2	2.54
4004	91	0.95	59.1	33.4	25.7	1.3	2.58
4005	91	0.60	57.5	32.5	25.0	1.3	2.61
4006	92	1.17	57.4	32.8	24.6	1.3	2.54
4007	92	0.93	55.1	30.9	24.2	1.3	2.45
4008	92	0.96	58.9	32.5	26.4	1.2	2.55
4009	92	1.18	56.6	32.2	24.4	1.3	2.58
4010	92	0.70	54.1	31.3	22.8	1.4	2.47
4011	120	0.56	55.4	30.9	24.5	1.3	2.47
4012	120	0.56	53.2	30.0	23.2	1.3	2.41
4013	120	0.49	54.3	30.2	24.1	1.3	2.51
4014	120	0.73	55.0	30.7	24.3	1.3	2.57
4015	120	0.86	56.3	31.3	25.0	1.3	2.51

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Biochemistry			
		NA (mmol/L)	K (mmol/L)	CL (mmol/L)	PHOS (mmol/L)
4001	91	139	4.4	99	1.63
4002	91	140	4.7	99	1.66
4003	91	140	4.3	100	2.10
4004	91	140	4.5	102	2.42
4005	91	142	4.4	105	2.33
4006	92	139	4.6	101	1.69
4007	92	141	4.2	104	1.79
4008	92	142	4.6	105	2.29
4009	92	141	4.1	102	2.50
4010	92	144	4.1	108	2.11
4011	120	143	3.9	106	1.87
4012	120	141	4.1	105	1.69
4013	120	143	4.5	106	2.36
4014	120	144	4.3	105	2.40
4015	120	143	4.3	105	2.35

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Biochemistry					
		AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	TBIL (umol/L)	BILEAC (umol/L)
1501	91	83	18	25	2 [a]	2.9	11.9
1502	91	119	23	36	2 [a]	3.3	10.9
1503	91	97	18	41	2 [a]	3.7	10.4
1504	91	130	31	46	2 [a]	3.6	76.4
1505	91	106	29	68	2 [a]	4.1	28.0
1506	92	83	15	22	2 [a]	3.0	13.3
1507	92	100	24	37	2 [a]	3.4	24.1
1508	92	92	21	29	2 [a]	3.5	37.6
1509	92	119	40	29	2 [a]	2.9	15.5
1510	92	110	26	44	2 [a]	3.7	32.4
1511	120	63	15	39	2 [a]	3.4	48.4
1512	120	77	16	37	2 [a]	3.1	73.6
1513	120	70	16	24	2 [a]	3.1	39.1
1514	120	78	18	36	2 [a]	3.1	19.7
1515	120	72	24	20	2 [a]	3.8	50.5

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Biochemistry					
		UREA (mmol/L)	CREAT (umol/L)	GLUC (mmol/L)	CHOL (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
1501	91	11.6	52	11.03	1.33	0.37	0.36 [a]
1502	91	5.0	40	8.44	1.38	0.40	0.36 [a]
1503	91	6.3	45	7.34	1.35	0.35	0.36 [a]
1504	91	5.8	44	9.67	1.28	0.39	0.36 [a]
1505	91	5.9	45	11.06	1.15	0.35	0.36 [a]
1506	92	7.2	49	9.42	1.56	0.51	0.36 [a]
1507	92	7.7	43	8.77	1.16	0.42	0.36 [a]
1508	92	7.3	41	8.19	2.21	0.71	0.36 [a]
1509	92	9.2	37	5.40	1.16	0.40	0.36 [a]
1510	92	8.2	40	5.95	1.68	0.54	0.36 [a]
1511	120	6.8	45	8.44	1.40	0.47	0.36 [a]
1512	120	7.8	43	9.84	1.32	0.47	0.36 [a]
1513	120	5.5	46	8.40	1.48	0.48	0.36 [a]
1514	120	8.8	44	8.53	0.96	0.31	0.36 [a]
1515	120	6.6	41	6.87	1.23	0.43	0.36 [a]

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Biochemistry					
		TRIG (mmol/L)	TPROT (g/L)	ALB (g/L)	GLOB (g/L)	A/G (ratio)	CA (mmol/L)
1501	91	0.49	59.6	36.4	23.2	1.6	2.53
1502	91	0.47	63.6	37.4	26.2	1.4	2.65
1503	91	0.41	63.9	36.7	27.2	1.3	2.55
1504	91	0.28	62.0	34.9	27.1	1.3	2.59
1505	91	0.25	60.1	34.6	25.5	1.4	2.54
1506	92	0.39	61.5	36.3	25.2	1.4	2.52
1507	92	0.27	64.2	37.6	26.6	1.4	2.57
1508	92	0.38	64.0	35.0	29.0	1.2	2.72
1509	92	0.25	63.9	37.3	26.6	1.4	2.67
1510	92	0.37	57.2	32.8	24.4	1.3	2.66
1511	120	0.44	59.0	34.8	24.2	1.4	2.43
1512	120	0.29	59.9	34.9	25.0	1.4	2.53
1513	120	0.50	63.4	38.2	25.2	1.5	2.58
1514	120	0.35	62.0	37.0	25.0	1.5	2.58
1515	120	0.34	66.0	37.9	28.1	1.3	2.69

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Biochemistry			
		NA (mmol/L)	K (mmol/L)	CL (mmol/L)	PHOS (mmol/L)
1501	91	136	3.9	100	1.87
1502	91	139	4.0	101	1.97
1503	91	140	3.9	104	2.05
1504	91	139	4.2	104	2.06
1505	91	138	4.2	103	1.84
1506	92	139	4.0	103	1.45
1507	92	139	4.3	102	2.05
1508	92	139	4.1	102	2.26
1509	92	141	4.1	106	2.05
1510	92	142	4.3	105	2.12
1511	120	140	3.2	103	1.91
1512	120	141	4.3	104	1.77
1513	120	141	4.1	102	1.70
1514	120	140	4.2	103	1.69
1515	120	142	4.1	104	2.02

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Biochemistry					
		AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	TBIL (umol/L)	BILEAC (umol/L)
2501	91	72	17	33	2 [a]	3.0	53.4
2502	91	86	26	47	2 [a]	3.1	37.0
2503	91	93	20	26	2 [a]	2.6	10.7
2504	91	119	23	31	2 [a]	2.7	40.6
2505	91	103	25	56	2 [a]	3.4	17.1
2506	92	74	17	36	2 [a]	2.9	12.5
2507	92	96	19	35	2 [a]	2.8	16.2
2508	92	98	22	50	2 [a]	3.3	25.3
2509	92	105	19	37	2 [a]	3.0	16.7
2510	92	138	17	28	2 [a]	3.3	9.0

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 20

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Biochemistry					
		UREA (mmol/L)	CREAT (umol/L)	GLUC (mmol/L)	CHOL (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
2501	91	7.4	47	9.47	2.38	0.56	0.36 [a]
2502	91	6.6	42	8.72	1.24	0.35	0.36 [a]
2503	91	5.0	38	5.98	1.22	0.35	0.36 [a]
2504	91	5.5	42	6.45	1.89	0.52	0.36 [a]
2505	91	6.3	45	7.69	1.83	0.45	0.36 [a]
2506	92	9.4	49	8.61	2.52	0.75	0.36 [a]
2507	92	8.7	45	7.87	1.42	0.51	0.36 [a]
2508	92	6.0	42	8.57	1.53	0.52	0.36 [a]
2509	92	7.9	46	6.35	1.80	0.56	0.36 [a]
2510	92	6.5	42	7.50	1.33	0.41	0.36 [a]

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 20

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Biochemistry					
		TRIG (mmol/L)	TPROT (g/L)	ALB (g/L)	GLOB (g/L)	A/G (ratio)	CA (mmol/L)
2501	91	0.36	62.9	35.1	27.8	1.3	2.55
2502	91	0.48	58.7	33.1	25.6	1.3	2.60
2503	91	0.82	62.5	36.2	26.3	1.4	2.70
2504	91	0.51	58.8	32.6	26.2	1.2	2.52
2505	91	0.35	61.8	35.6	26.2	1.4	2.61
2506	92	0.57	63.2	35.6	27.6	1.3	2.51
2507	92	0.45	61.7	36.4	25.3	1.4	2.60
2508	92	0.53	62.1	35.0	27.1	1.3	2.62
2509	92	0.53	61.1	34.7	26.4	1.3	2.57
2510	92	0.38	60.7	36.2	24.5	1.5	2.47

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Biochemistry			
		NA (mmol/L)	K (mmol/L)	CL (mmol/L)	PHOS (mmol/L)
2501	91	137	4.0	101	1.87
2502	91	140	4.1	103	2.08
2503	91	142	4.2	104	1.95
2504	91	139	3.9	103	1.82
2505	91	139	4.2	104	1.79
2506	92	139	3.3	100	1.74
2507	92	138	3.9	100	1.97
2508	92	143	3.8	103	1.99
2509	92	142	4.0	104	1.87
2510	92	142	4.0	106	1.40

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Biochemistry					
		AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	TBIL (umol/L)	BILEAC (umol/L)
3501	91	78	26	50	2 [a]	2.6	39.3
3502	91	92	26	53	2 [a]	3.7	39.5
3503	91	125	21	10	2 [a]	3.5	10.7
3504	91	115	22	26	2 [a]	4.0	18.3
3505	91	97	26	53	2 [a]	5.3	28.0
3506	92	84	22	35	2 [a]	3.1	15.5
3507	92	108	21	24	2 [a]	3.3	5.6
3508	92	112	28	21	2 [a]	2.8	8.5
3509	92	122	34	69	2 [a]	3.3	21.4
3510	92	122	22	34	2 [a]	3.1	35.4

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Biochemistry					
		UREA (mmol/L)	CREAT (umol/L)	GLUC (mmol/L)	CHOL (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
3501	91	6.3	46	11.41	1.69	0.48	0.36 [a]
3502	91	6.5	41	10.30	2.20	0.55	0.36 [a]
3503	91	7.4	44	6.49	1.65	0.43	0.36 [a]
3504	91	6.8	45	4.47	1.26	0.35	0.36 [a]
3505	91	3.9	41	8.70	1.71	0.50	0.36 [a]
3506	92	6.9	37	6.69	1.58	0.51	0.36 [a]
3507	92	6.3	39	7.24	2.08	0.67	0.36 [a]
3508	92	7.4	39	5.08	1.45	0.47	0.36 [a]
3509	92	9.0	45	7.41	1.78	0.55	0.36 [a]
3510	92	5.7	38	6.81	2.25	0.71	0.36 [a]

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Biochemistry					
		TRIG (mmol/L)	TPROT (g/L)	ALB (g/L)	GLOB (g/L)	A/G (ratio)	CA (mmol/L)
3501	91	0.56	55.7	30.8	24.9	1.2	2.53
3502	91	0.33	62.6	34.0	28.6	1.2	2.59
3503	91	0.34	72.2	42.7	29.5	1.4	2.68
3504	91	0.43	62.5	35.7	26.8	1.3	2.58
3505	91	0.48	69.1	40.0	29.1	1.4	2.73
3506	92	0.42	63.3	37.9	25.4	1.5	2.67
3507	92	0.90	65.3	38.4	26.9	1.4	2.59
3508	92	0.41	56.7	32.0	24.7	1.3	2.52
3509	92	0.64	61.6	34.7	26.9	1.3	2.65
3510	92	0.50	66.0	37.0	29.0	1.3	2.72

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Biochemistry			
		NA (mmol/L)	K (mmol/L)	CL (mmol/L)	PHOS (mmol/L)
3501	91	138	5.0	106	1.97
3502	91	139	4.2	102	2.06
3503	91	141	3.7	104	1.61
3504	91	141	4.2	104	1.99
3505	91	140	3.9	103	1.84
3506	92	140	4.4	104	2.68
3507	92	141	4.3	105	2.14
3508	92	144	4.2	107	2.04
3509	92	143	3.7	103	2.16
3510	92	142	4.3	106	2.04

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Biochemistry					
		AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	TBIL (umol/L)	BILEAC (umol/L)
4501	91	79	27	96	2 [a]	4.5	17.8
4502	91	103	24	61	2 [a]	4.6	24.1
4503	91	81	30	41	2 [a]	4.1	21.0
4504	91	158	38	74	2 [a]	3.7	36.3
4505	91	100	32	68	2 [a]	3.5	83.8
4506	92	101	20	41	2 [a]	4.2	30.7
4507	92	61	17	27	2 [a]	2.7	29.6
4508	92	99	26	29	2 [a]	3.6	22.1
4509	92	123	28	60	2 [a]	3.4	10.2
4510	92	82	23	48	2 [a]	4.1	50.2
4511	120	60	17	34	2 [a]	3.4	20.3
4512	120	145	21	28	2 [a]	2.7	10.1
4513	120	118	41	60	2 [a]	3.7	38.0
4514	120	151	31	43	2 [a]	4.0	294.0
4515	120	95	23	10 [a]	2 [a]	3.0	57.6

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Biochemistry					
		UREA (mmol/L)	CREAT (umol/L)	GLUC (mmol/L)	CHOL (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
4501	91	6.4	36	9.39	1.27	0.38	0.36 [a]
4502	91	5.3	40	11.12	1.68	0.48	0.36 [a]
4503	91	6.4	43	11.54	0.91	0.27	0.36 [a]
4504	91	7.2	41	8.06	1.37	0.41	0.36 [a]
4505	91	6.3	39	7.89	1.58	0.45	0.36 [a]
4506	92	5.8	37	6.01	1.56	0.51	0.36 [a]
4507	92	7.9	42	8.21	2.02	0.61	0.36 [a]
4508	92	7.1	38	4.96	1.48	0.47	0.36 [a]
4509	92	7.2	42	8.80	1.68	0.54	0.36 [a]
4510	92	9.7	39	5.78	2.28	0.69	0.36 [a]
4511	120	8.6	49	10.77	1.30	0.42	0.36 [a]
4512	120	11.9	44	6.96	1.31	0.45	0.36 [a]
4513	120	6.2	42	8.04	1.10	0.39	0.36 [a]
4514	120	7.2	47	7.19	1.82	0.53	0.36 [a]
4515	120	7.4	41	9.46	2.24	0.67	0.36 [a]

[a] [RC:Assigned value below the reportable range]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Biochemistry					
		TRIG (mmol/L)	TPROT (g/L)	ALB (g/L)	GLOB (g/L)	A/G (ratio)	CA (mmol/L)
4501	91	0.26	61.1	36.2	24.9	1.5	2.59
4502	91	0.46	62.8	37.2	25.6	1.5	2.65
4503	91	0.43	58.7	35.0	23.7	1.5	2.58
4504	91	0.52	59.3	32.5	26.8	1.2	2.58
4505	91	0.49	61.9	34.4	27.5	1.3	2.57
4506	92	0.48	61.5	35.0	26.5	1.3	2.63
4507	92	0.39	60.2	33.6	26.6	1.3	2.66
4508	92	0.61	64.5	36.2	28.3	1.3	2.68
4509	92	0.33	62.5	35.4	27.1	1.3	2.51
4510	92	0.71	64.0	37.8	26.2	1.4	2.66
4511	120	0.34	59.9	34.3	25.6	1.3	2.56
4512	120	0.36	58.5	34.4	24.1	1.4	2.62
4513	120	0.40	56.9	31.8	25.1	1.3	2.55
4514	120	0.29	59.1	33.2	25.9	1.3	2.55
4515	120	0.38	60.9	34.1	26.8	1.3	2.56

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Individual Clinical Chemistry Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Biochemistry			
		NA (mmol/L)	K (mmol/L)	CL (mmol/L)	PHOS (mmol/L)
4501	91	141	4.3	105	2.53
4502	91	141	3.9	104	2.38
4503	91	141	4.2	103	2.30
4504	91	140	4.3	104	2.06
4505	91	140	4.3	102	2.41
4506	92	143	4.0	104	2.25
4507	92	141	3.9	105	2.29
4508	92	143	4.0	105	2.46
4509	92	143	3.6	104	1.99
4510	92	143	4.2	105	2.00
4511	120	140	3.8	103	1.85
4512	120	139	4.2	103	2.50
4513	120	140	4.2	102	2.03
4514	120	138	4.4	104	2.00
4515	120	139	3.9	103	1.67

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Test Facility Study No. (b) (4)

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Individual Urinalysis Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Urinalysis					
		VOLUME (mL)	COLOR	CLARITY	GLUC	BIL	KET
1001	91	10.2	LY	Tur	Neg	Neg	1+
1002	91	22.9	LY	Tur	Neg	Neg	1+
1003	91	5.7	LY	Tur	Neg	Neg	1+
1004	91	28.7	LY	Tur	Neg	Neg	1+
1005	91	19.0	LY	Tur	Neg	Neg	1+
1006	92	14.3	LY	Cld	Neg	Neg	1+
1007	92	13.8	LY	Tur	Neg	Neg	1+
1008	92	28.3	LY	Cld	Neg	Neg	Neg
1009	92	13.7	LY	Tur	Neg	Neg	1+
1010	92	22.5	LY	Tur	Neg	Neg	Neg
1011	120	19.9	LY	Cld	Neg	Neg	1+
1012	120	21.2	LY	Clr	Neg	Neg	1+
1013	120	22.5	LY	Clr	Neg	Neg	1+
1014	120	23.7	LY	Cld	Neg	Neg	Neg
1015	120	9.1	DY	Clr	Neg	Neg	2+

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Urinalysis Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Urinalysis					
		SPECIFIC GRAVITY	OSMLTY (mOsm/kg)	BLD	URINE pH	PROT	NIT
1001	91	1.024	802	Neg	7.0	1+	Neg
1002	91	1.014	426	Neg	7.5	Neg	Neg
1003	91	1.032	1112	Neg	7.5	2+	Pos
1004	91	1.010	362	Neg	7.5	Neg	Pos
1005	91	1.014	398	Neg	8.5	1+	Neg
1006	92	1.021	730	Neg	7.0	1+	Pos
1007	92	1.019	628	Neg	8.0	1+	Pos
1008	92	1.012	316	Neg	7.5	Neg	Neg
1009	92	1.017	536	Neg	8.5	1+	Neg
1010	92	1.012	376	Neg	9.0 [a]	1+	Neg
1011	120	1.016	456	Neg	7.5	Neg	Neg
1012	120	1.010	404	Neg	7.0	Neg	Neg
1013	120	1.014	352	Neg	7.5	1+	Neg
1014	120	1.012	380	Neg	7.0	Neg	Neg
1015	120	1.029	974	Neg	6.5	2+	Neg

[a] [RC:Assigned value above the reportable range]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Individual Urinalysis Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Urinalysis					
		URINE MICROSCOPIC	EPIC (HPF)	BACT (HPF)	CAOX CRYS (HPF)	CACO CRYS (HPF)	TPHOS CRYS (HPF)
1001	91	-	-	3+	-	-	1+
1002	91	-	-	3+	-	-	-
1003	91	-	-	2+	-	-	1+
1004	91	-	-	2+	-	-	3+
1005	91	-	-	3+	-	-	3+
1006	92	-	-	3+	-	-	1+
1007	92	-	-	4+	-	-	1+
1008	92	-	-	2+	-	-	2+
1009	92	-	-	3+	-	-	2+
1010	92	-	-	2+	-	-	2+
1011	120	-	-	1+	-	-	-
1012	120	-	-	2+	-	-	1+
1013	120	-	-	2+	-	-	-
1014	120	-	-	3+	-	-	3+
1015	120	-	-	1+	-	1+	1+

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Urinalysis Values

(b) (4)

Sex: Male

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Urinalysis		
		AMPH CRYS (HPF)	SPERM (LPF)	OTHER
1001	91	-	1+	-
1002	91	-	1+	-
1003	91	-	-	-
1004	91	-	-	-
1005	91	-	-	-
1006	92	-	-	-
1007	92	-	1+	-
1008	92	-	-	-
1009	92	-	1+	-
1010	92	-	-	-
1011	120	-	-	-
1012	120	1+	-	-
1013	120	-	-	-
1014	120	-	-	1+ [a]
1015	120	1+	1+	-

[a] [RC:Sodium urate crystals]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Urinalysis Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Urinalysis					
		VOLUME (mL)	COLOR	CLARITY	GLUC	BIL	KET
2001	91	17.0	LY	Cld	Neg	Neg	1+
2002	91	17.7	LY	Cld	Neg	Neg	1+
2003	91	22.5	LY	Cld	Neg	Neg	1+
2004	91	23.4	LY	Tur	Neg	Neg	Neg
2005	91	7.3	DY	Cld	Neg	Neg	2+
2006	92	13.6	LY	Tur	Neg	Neg	2+
2007	92	13.2	LY	Cld	Neg	Neg	1+
2008	92	19.6	LY	Tur	Neg	Neg	1+
2009	92	11.8	LY	Cld	Neg	Neg	1+
2010	92	19.2	LY	Cld	Neg	Neg	Neg

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Individual Urinalysis Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Urinalysis					
		SPECIFIC GRAVITY	OSMLTY (mOsm/kg)	BLD	URINE pH	PROT	NIT
2001	91	1.018	558	Neg	7.0	1+	Pos
2002	91	1.020	566	Neg	7.0	1+	Neg
2003	91	1.015	486	Neg	7.0	1+	Pos
2004	91	1.013	414	Neg	8.5	1+	Pos
2005	91	1.038	1244	Neg	6.5	2+	Neg
2006	92	1.020	648	Neg	8.0	1+	Pos
2007	92	1.021	616	Neg	7.5	1+	Neg
2008	92	1.012	440	Neg	8.5	1+	Neg
2009	92	1.027	838	Neg	7.0	1+	Neg
2010	92	1.015	464	Neg	7.0	Neg	Pos

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Individual Urinalysis Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Urinalysis					
		URINE MICROSCOPIC	EPIC (HPF)	BACT (HPF)	CAOX CRYS (HPF)	CACO CRYS (HPF)	TPHOS CRYS (HPF)
2001	91	-	-	3+	-	-	2+
2002	91	-	-	2+	-	-	1+
2003	91	-	-	2+	-	-	2+
2004	91	-	-	2+	-	-	3+
2005	91	-	-	1+	-	-	-
2006	92	-	1+	3+	-	-	3+
2007	92	-	-	2+	-	-	1+
2008	92	-	-	3+	-	-	1+
2009	92	-	-	2+	-	-	1+
2010	92	-	-	3+	-	-	2+

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Urinalysis Values

(b) (4)

Sex: Male

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Urinalysis		
		AMPH CRYS (HPF)	SPERM (LPF)	OTHER
2001	91	-	1+	-
2002	91	-	-	-
2003	91	-	-	-
2004	91	-	-	-
2005	91	-	-	-
2006	92	-	2+	-
2007	92	-	1+	-
2008	92	-	1+	-
2009	92	-	-	-
2010	92	-	2+	-

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Test Facility Study No. (b) (4)

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Individual Urinalysis Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Urinalysis					
		VOLUME (mL)	COLOR	CLARITY	GLUC	BIL	KET
3001	91	15.7	DY	Cld	Neg	Neg	1+
3002	91	15.6	DY	Cld	Neg	Neg	1+
3003	91	20.0	LY	Cld	Neg	Neg	Neg
3004	91	11.0	DY	Cld	Neg	Neg	2+
3005	91	26.4	LY	Cld	Neg	Neg	1+
3006	92	18.8	LY	Cld	Neg	Neg	1+
3007	92	13.3	LY	Cld	Neg	Neg	1+
3008	92	14.7	LY	Tur	Neg	Neg	1+
3009	92	18.6	LY	Cld	Neg	Neg	Neg
3010	92	8.3	LY	Tur	Neg	Neg	1+

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Individual Urinalysis Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Urinalysis					
		SPECIFIC GRAVITY	OSMLTY (mOsm/kg)	BLD	URINE pH	PROT	NIT
3001	91	1.023	712	Neg	7.0	1+	Neg
3002	91	1.023	694	Neg	6.5	1+	Neg
3003	91	1.018	510	Neg	8.0	1+	Pos
3004	91	1.027	848	Neg	6.5	1+	Neg
3005	91	1.010	278	Neg	6.5	Neg	Pos
3006	92	1.019	520	Neg	6.5	1+	Neg
3007	92	1.019	526	Neg	6.0	Neg	Neg
3008	92	1.017	462	Neg	6.5	1+	Neg
3009	92	1.017	496	Neg	6.5	1+	Neg
3010	92	1.028	866	Neg	7.0	2+	Neg

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Urinalysis Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Urinalysis					
		URINE MICROSCOPIC	EPIC (HPF)	BACT (HPF)	CAOX CRYS (HPF)	CACO CRYS (HPF)	TPHOS CRYS (HPF)
3001	91	-	-	3+	-	-	-
3002	91	-	-	1+	-	-	-
3003	91	-	-	2+	-	-	2+
3004	91	-	-	3+	-	-	-
3005	91	-	-	4+	-	-	-
3006	92	-	-	2+	-	-	-
3007	92	-	-	2+	-	-	-
3008	92	-	-	2+	-	-	-
3009	92	-	-	2+	-	-	-
3010	92	-	-	3+	-	-	-

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Individual Urinalysis Values

(b) (4)

Sex: Male

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Urinalysis		
		AMPH CRYS (HPF)	SPERM (LPF)	OTHER
3001	91	-	-	-
3002	91	-	-	-
3003	91	1+	1+	-
3004	91	-	1+	-
3005	91	-	-	-
3006	92	-	1+	-
3007	92	-	1+	-
3008	92	-	2+	-
3009	92	-	1+	-
3010	92	-	2+	-

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Individual Urinalysis Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Urinalysis					
		VOLUME (mL)	COLOR	CLARITY	GLUC	BIL	KET
4001	91	52.2	LY	Cld	Neg	Neg	1+
4002	91	13.4	LY	Cld	Neg	Neg	2+
4003	91	36.5	LY	Cld	Neg	Neg	1+
4004	91	15.7	DY	Cld	Neg	Neg	2+
4005	91	18.6	DY	Cld	Neg	Neg	1+
4006	92	6.9	DY	Cld	Neg	1+	2+
4007	92	12.2	DY	Cld	Neg	1+	2+
4008	92	15.9	DY	Cld	Neg	1+	2+
4009	92	9.4	DY	Cld	Neg	2+	2+
4010	92	10.0	DY	Cld	Neg	1+	2+
4011	120	26.0	LY	Cld	Neg	Neg	Neg
4012	120	19.4	LY	Cld	Neg	Neg	Neg
4013	120	9.3	DY	Cld	Neg	Neg	2+
4014	120	3.4	Or	Cld	Neg	1+	1+
4015	120	11.6	LY	Cld	Neg	Neg	1+

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Individual Urinalysis Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Urinalysis					
		SPECIFIC GRAVITY	OSMLTY (mOsm/kg)	BLD	URINE pH	PROT	NIT
4001	91	1.012	264	Neg	6.0	Neg	Neg
4002	91	1.027	716	Neg	5.0	1+	Neg
4003	91	1.013	294	Neg	5.5	Neg	Neg
4004	91	1.022	644	Neg	6.5	1+	Neg
4005	91	1.021	558	Neg	5.5	Neg	Neg
4006	92	1.035	1070	Neg	5.5	2+	Neg
4007	92	1.029	844	Neg	5.0	1+	Neg
4008	92	1.026	722	Neg	5.0	1+	Neg
4009	92	1.033	954	Neg	5.0	1+	Neg
4010	92	1.033	882	Neg	5.5	1+	Neg
4011	120	1.011	278	Neg	7.0	Neg	Neg
4012	120	1.014	394	Neg	8.0	Neg	Pos
4013	120	1.025	782	Neg	7.0	2+	Neg
4014	120	1.045	1544	Neg	6.0	3+	Neg
4015	120	1.019	568	Neg	6.5	1+	Neg

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Individual Urinalysis Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Urinalysis					
		URINE MICROSCOPIC	EPIC (HPF)	BACT (HPF)	CAOX CRYS (HPF)	CACO CRYS (HPF)	TPHOS CRYS (HPF)
4001	91	-	-	2+	-	-	-
4002	91	-	-	1+	-	-	-
4003	91	-	-	1+	-	-	-
4004	91	-	-	1+	-	-	-
4005	91	-	-	1+	-	-	-
4006	92	-	-	1+	-	-	-
4007	92	-	-	1+	-	-	-
4008	92	-	-	1+	-	-	-
4009	92	-	-	1+	-	-	-
4010	92	-	-	1+	-	-	-
4011	120	-	-	3+	-	-	1+
4012	120	-	-	3+	-	-	1+
4013	120	-	-	3+	-	1+	1+
4014	120	-	-	1+	-	2+	-
4015	120	-	-	1+	-	-	-

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Individual Urinalysis Values

(b) (4)

Sex: Male

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Urinalysis		
		AMPH CRYS (HPF)	SPERM (LPF)	OTHER
4001	91	-	2+	-
4002	91	-	-	-
4003	91	-	-	-
4004	91	-	-	-
4005	91	-	-	-
4006	92	-	1+	-
4007	92	-	1+	-
4008	92	-	-	-
4009	92	-	1+	-
4010	92	-	-	-
4011	120	1+	-	-
4012	120	1+	-	-
4013	120	1+	1+	-
4014	120	1+	-	-
4015	120	1+	-	-

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Individual Urinalysis Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Urinalysis					
		VOLUME (mL)	COLOR	CLARITY	GLUC	BIL	KET
1501	91	9.9	LY	Tur	Neg	Neg	Neg
1502	91	5.4	LY	Cld	Neg	Neg	Neg
1503	91	30.1	LY	Cld	Neg	Neg	Neg
1504	91	20.1	LY	Tur	Neg	Neg	Neg
1505	91	20.1	LY	Tur	Neg	Neg	Neg
1506	92	14.7	LY	Cld	Neg	Neg	Neg
1507	92	18.3	LY	Cld	Neg	Neg	Neg
1508	92	10.3	LY	Tur	Neg	Neg	Neg
1509	92	5.8	LY	Cld	Neg	Neg	Neg
1510	92	8.5	LY	Cld	Neg	Neg	Neg
1511	120	12.3	LY	Clr	Neg	Neg	Neg
1512	120	15.1	LY	Cld	Neg	Neg	Neg
1513	120	8.8	DY	Clr	Neg	Neg	Neg
1514	120	4.8	DY	Cld	Neg	Neg	Neg
1515	120	11.9	LY	Clr	Neg	Neg	Neg

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Individual Urinalysis Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Urinalysis					
		SPECIFIC GRAVITY	OSMLTY (mOsm/kg)	BLD	URINE pH	PROT	NIT
1501	91	1.022	876	Neg	7.5	Neg	Pos
1502	91	1.031	960	Neg	7.0	1+	Neg
1503	91	1.010	262	Neg	7.0	Neg	Pos
1504	91	1.013	468	Neg	7.5	Neg	Pos
1505	91	1.013	440	Neg	7.0	Neg	Neg
1506	92	1.012	366	Neg	5.5	Neg	Neg
1507	92	1.010	424	Neg	7.0	Neg	Pos
1508	92	1.022	822	Neg	8.0	Neg	Pos
1509	92	1.022	784	Neg	6.0	Neg	Neg
1510	92	1.019	738	Neg	7.0	Neg	Neg
1511	120	1.018	570	Neg	6.5	Neg	Neg
1512	120	1.014	430	Neg	6.5	Neg	Neg
1513	120	1.022	676	Neg	7.0	Neg	Neg
1514	120	1.033	1228	Neg	6.5	1+	Neg
1515	120	1.016	500	Neg	6.5	Neg	Neg

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Individual Urinalysis Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Urinalysis					
		URINE MICROSCOPIC	EPIC (HPF)	BACT (HPF)	CAOX CRYS (HPF)	CACO CRYS (HPF)	TPHOS CRYS (HPF)
1501	91	-	-	2+	-	-	3+
1502	91	-	-	3+	-	-	1+
1503	91	-	-	3+	-	-	2+
1504	91	-	-	2+	-	-	2+
1505	91	-	-	3+	-	-	2+
1506	92	-	-	2+	-	-	1+
1507	92	-	-	2+	-	-	2+
1508	92	-	-	3+	-	-	2+
1509	92	-	-	1+	-	-	-
1510	92	-	-	2+	-	-	1+
1511	120	-	-	1+	-	-	-
1512	120	-	-	2+	-	-	-
1513	120	-	-	3+	1+	-	1+
1514	120	-	-	4+	-	-	1+
1515	120	-	-	2+	-	-	-

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Individual Urinalysis Values

(b) (4)

Sex: Female

0 mg/kg /day Group 1	Day(s) Relative to Start Date	Reporting Urinalysis		
		AMPH CRYS (HPF)	SPERM (LPF)	OTHER
1501	91	2+	-	-
1502	91	-	-	-
1503	91	-	-	-
1504	91	2+	-	-
1505	91	-	-	-
1506	92	-	-	-
1507	92	1+	-	-
1508	92	-	-	-
1509	92	-	-	-
1510	92	-	-	-
1511	120	-	-	-
1512	120	1+	-	-
1513	120	1+	-	-
1514	120	2+	-	-
1515	120	1+	-	-

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Individual Urinalysis Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Urinalysis					
		VOLUME (mL)	COLOR	CLARITY	GLUC	BIL	KET
2501	91	18.2	LY	Tur	Neg	Neg	Neg
2502	91	11.9	LY	Tur	Neg	Neg	Neg
2503	91	17.7	LY	Cld	Neg	Neg	Neg
2504	91	13.8	LY	Cld	Neg	Neg	Neg
2505	91	4.1	DY	Cld	Neg	1+	1+
2506	92	26.0	LY	Cld	Neg	Neg	Neg
2507	92	10.9	LY	Cld	Neg	Neg	Neg
2508	92	6.3	LY	Cld	Neg	Neg	1+
2509	92	6.1	LY	Cld	Neg	Neg	Neg
2510	92	6.5	LY	Cld	Neg	Neg	Neg

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Individual Urinalysis Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Urinalysis					
		SPECIFIC GRAVITY	OSMLTY (mOsm/kg)	BLD	URINE pH	PROT	NIT
2501	91	1.012	410	Neg	7.5	Neg	Pos
2502	91	1.018	690	Neg	7.5	Neg	Neg
2503	91	1.013	402	Neg	7.0	Neg	Pos
2504	91	1.023	842	Neg	7.0	Neg	Neg
2505	91	1.044	1602	Neg	6.5	1+	Neg
2506	92	1.013	382	Neg	6.5	Neg	Pos
2507	92	1.018	552	Neg	6.5	Neg	Neg
2508	92	1.030	990	Neg	6.5	Neg	Neg
2509	92	1.027	914	Neg	6.0	Neg	Neg
2510	92	1.029	1020	Neg	5.5	Neg	Neg

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Individual Urinalysis Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Urinalysis					
		URINE MICROSCOPIC	EPIC (HPF)	BACT (HPF)	CAOX CRYS (HPF)	CACO CRYS (HPF)	TPHOS CRYS (HPF)
2501	91	-	-	2+	-	-	2+
2502	91	-	-	2+	-	-	1+
2503	91	-	-	4+	-	-	1+
2504	91	-	-	3+	-	-	3+
2505	91	-	-	1+	-	-	-
2506	92	-	-	2+	-	-	2+
2507	92	-	-	2+	-	-	2+
2508	92	-	-	1+	-	-	-
2509	92	-	-	2+	-	-	-
2510	92	-	-	1+	-	-	-

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Individual Urinalysis Values

(b) (4)

Sex: Female

500 mg/kg /day Group 2	Day(s) Relative to Start Date	Reporting Urinalysis		
		AMPH CRYS (HPF)	SPERM (LPF)	OTHER
2501	91	2+	-	-
2502	91	3+	-	-
2503	91	-	-	-
2504	91	-	-	-
2505	91	1+	-	-
2506	92	4+	-	-
2507	92	-	-	-
2508	92	-	-	-
2509	92	-	-	-
2510	92	-	-	-

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Individual Urinalysis Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Urinalysis					
		VOLUME (mL)	COLOR	CLARITY	GLUC	BIL	KET
3501	91	7.1	LY	Tur	Neg	Neg	1+
3502	91	10.8	LY	Cld	Neg	Neg	Neg
3503	91	20.7	LY	Cld	Neg	Neg	Neg
3504	91	29.1	LY	Cld	Neg	Neg	Neg
3505	91	24.0	LY	Cld	Neg	Neg	Neg
3506	92	10.5	LY	Cld	Neg	Neg	1+
3507	92	10.6	LY	Cld	Neg	Neg	Neg
3508	92	10.5	LY	Cld	Neg	Neg	1+
3509	92	4.5	DY	Cld	Neg	1+	1+
3510	92	14.7	LY	Cld	Neg	Neg	Neg

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Individual Urinalysis Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Urinalysis					
		SPECIFIC GRAVITY	OSMLTY (mOsm/kg)	BLD	URINE pH	PROT	NIT
3501	91	1.031	1058	Neg	7.0	1+	Pos
3502	91	1.021	734	Neg	7.0	Neg	Pos
3503	91	1.013	414	Neg	6.0	Neg	Pos
3504	91	1.012	350	Neg	7.0	Neg	Pos
3505	91	1.011	328	Neg	7.0	Neg	Pos
3506	92	1.023	690	Neg	6.5	Neg	Neg
3507	92	1.022	702	Neg	5.5	Neg	Neg
3508	92	1.024	764	Neg	6.0	Neg	Neg
3509	92	1.041	1430	Neg	5.5	1+	Neg
3510	92	1.019	512	Neg	6.5	Neg	Neg

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Individual Urinalysis Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Urinalysis					
		URINE MICROSCOPIC	EPIC (HPF)	BACT (HPF)	CAOX CRYS (HPF)	CACO CRYS (HPF)	TPHOS CRYS (HPF)
3501	91	-	-	3+	-	-	1+
3502	91	-	-	2+	-	-	2+
3503	91	-	-	4+	-	-	-
3504	91	-	-	2+	-	-	2+
3505	91	-	-	3+	-	-	1+
3506	92	-	-	1+	-	-	-
3507	92	-	-	3+	-	-	-
3508	92	-	-	1+	-	-	-
3509	92	-	-	1+	-	-	-
3510	92	-	-	2+	-	-	-

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Individual Urinalysis Values

(b) (4)

Sex: Female

1000 mg/kg /day Group 3	Day(s) Relative to Start Date	Reporting Urinalysis		
		AMPH CRYS (HPF)	SPERM (LPF)	OTHER
3501	91	-	-	-
3502	91	2+	-	-
3503	91	-	-	-
3504	91	-	-	-
3505	91	1+	-	-
3506	92	-	-	-
3507	92	-	-	-
3508	92	-	-	-
3509	92	-	-	-
3510	92	-	-	-

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Individual Urinalysis Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Urinalysis					
		VOLUME (mL)	COLOR	CLARITY	GLUC	BIL	KET
4501	91	11.2	DY	Cld	Neg	1+	1+
4502	91	36.6	DY	Cld	Neg	Neg	Neg
4503	91	13.9	DY	Cld	Neg	1+	1+
4504	91	7.1	DY	Cld	Neg	1+	1+
4505	91	21.2	LY	Cld	Neg	Neg	Neg
4506	92	36.1	LY	Cld	Neg	Neg	Neg
4507	92	6.5	LY	Cld	Neg	1+	1+
4508	92	19.1	LY	Cld	Neg	Neg	1+
4509	92	7.7	LY	Cld	Neg	1+	1+
4510	92	24.7	LY	Cld	Neg	Neg	Neg
4511	120	7.7	DY	Clr	Neg	Neg	Neg
4512	120	22.2	LY	Clr	Neg	Neg	Neg
4513	120	11.7	LY	Clr	Neg	Neg	Neg
4514	120	15.5	LY	Clr	Neg	Neg	Neg
4515	120	6.1	DY	Clr	Neg	Neg	1+

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Individual Urinalysis Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Urinalysis					
		SPECIFIC GRAVITY	OSMLTY (mOsm/kg)	BLD	URINE pH	PROT	NIT
4501	91	1.022	622	Neg	6.0	Neg	Neg
4502	91	1.010	240	Neg	6.5	Neg	Pos
4503	91	1.023	594	Neg	5.5	Neg	Neg
4504	91	1.032	930	Neg	5.5	Neg	Neg
4505	91	1.017	504	Neg	6.0	Neg	Neg
4506	92	1.008	224	Neg	6.0	Neg	Neg
4507	92	1.035	1140	Neg	5.5	1+	Neg
4508	92	1.061 [a]	416	Neg	5.5	Neg	Neg
4509	92	1.034	1024	Neg	5.5	Neg	Neg
4510	92	1.014	316	Neg	5.5	Neg	Neg
4511	120	1.024	822	Neg	6.0	Neg	Neg
4512	120	1.012	362	Neg	6.0	Neg	Neg
4513	120	1.015	482	Neg	7.0	Neg	Neg
4514	120	1.018	504	Neg	6.5	Neg	Neg
4515	120	1.031	962	Neg	6.0	1+	Neg

[a] [RC:Assigned value above the reportable range]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 21

24-Feb-2023 08:42:18

Individual Urinalysis Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Urinalysis					
		URINE MICROSCOPIC	EPIC (HPF)	BACT (HPF)	CAOX CRYS (HPF)	CACO CRYS (HPF)	TPHOS CRYS (HPF)
4501	91	-	-	1+	-	-	-
4502	91	-	-	3+	-	-	-
4503	91	-	-	1+	-	-	-
4504	91	NAF	-	-	-	-	-
4505	91	-	-	1+	-	-	-
4506	92	-	-	1+	-	-	-
4507	92	-	-	1+	-	-	-
4508	92	-	-	1+	-	-	-
4509	92	-	-	1+	-	-	-
4510	92	-	-	1+	-	-	-
4511	120	-	-	2+	-	-	-
4512	120	-	-	1+	-	-	-
4513	120	-	-	2+	-	-	-
4514	120	-	-	2+	-	-	-
4515	120	-	-	1+	-	-	-

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 21

24-Feb-2023 08:42:18

Individual Urinalysis Values

(b) (4)

Sex: Female

2000 mg/kg /day Group 4	Day(s) Relative to Start Date	Reporting Urinalysis		
		AMPH CRYS (HPF)	SPERM (LPF)	OTHER
4501	91	-	-	-
4502	91	-	-	-
4503	91	-	-	-
4504	91	-	-	-
4505	91	-	-	-
4506	92	-	-	-
4507	92	-	-	-
4508	92	-	-	-
4509	92	-	-	-
4510	92	-	-	-
4511	120	1+	-	-
4512	120	-	-	-
4513	120	-	-	-
4514	120	-	-	-
4515	120	-	-	-

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 22

16-Mar-2023 09:10:51

Individual Estrous Cycle Stage at Necropsy: Main Females

(b) (4)

Sex: Female Stage of Estrous at Necropsy

0 mg/kg /day Group 1	Day(s) Relative to Start Date
	91 or 92
1501	P
1502	M
1503	E
1504	D
1505	D
1506	D
1507	D
1508	E
1509	M
1510	D

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 22

16-Mar-2023 09:10:51

Individual Estrous Cycle Stage at Necropsy: Main Females

(b) (4)

Sex: Female Stage of Estrous at Necropsy

500 mg/kg /day Group 2	Day(s) Relative to Start Date
	91 or 92
2501	D
2502	M
2503	D
2504	E
2505	M
2506	P
2507	D
2508	E
2509	M
2510	E

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 22

16-Mar-2023 09:10:51

Individual Estrous Cycle Stage at Necropsy: Main Females

(b) (4)

Sex: Female Stage of Estrous at Necropsy

1000 mg/kg /day Group 3	Day(s) Relative to Start Date
	91 or 92
3501	E
3502	D
3503	D
3504	M
3505	P
3506	D
3507	D
3508	D
3509	M
3510	D

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 22

16-Mar-2023 09:10:51

Individual Estrous Cycle Stage at Necropsy: Main Females

(b) (4)

Sex: Female Stage of Estrous at Necropsy

2000 mg/kg /day Group 4	Day(s) Relative to Start Date
	91 or 92
4501	P
4502	D
4503	D
4504	D
4505	M
4506	P
4507	E
4508	M
4509	E
4510	D

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 22

16-Mar-2023 09:12:51

Individual Estrous Cycle Stage at Necropsy: Recovery Females

(b) (4)

Sex: Female Stage of Estrous at Necropsy

0 mg/kg /day Group 1	Day(s) Relative to Start Date
	120
1511	E
1512	M
1513	D
1514	E
1515	D

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 22

16-Mar-2023 09:12:51

Individual Estrous Cycle Stage at Necropsy: Recovery Females

(b) (4)

Sex: Female Stage of Estrous at Necropsy

2000 mg/kg /day Group 4	Day(s) Relative to Start Date
	120
4511	P
4512	P
4513	E
4514	D
4515	E

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 23

(b) (4)

Individual Sperm Motility Data - Main Males
(From the Epididymis)

Group 1: 0 mg/kg/day

Male Number	Total Number of Sperm	Motile Sperm Count	Motile Sperm (%)	Progressive Sperm Count	Progressive Sperm (%)
1001	726	678	93	488	67
1002	1041	1038	100	824	79
1003	1394	1369	98	1031	74
1004	1384	1373	99	966	70
1005	1061	1046	99	793	75
1006	730	716	98	524	72
1007	1201	1185	99	866	72
1008	1092	1064	97	770	71
1009	1184	1162	98	793	67
1010	597	555	93	445	75
Mean	1041	1019	97	750	72
SD	276	283	2	200	4
N	10	10	10	10	10

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 23

(b) (4)

Individual Sperm Motility Data - Main Males
(From the Epididymis)

Group 2: 500 mg/kg/day

Male Number	Total Number of Sperm	Motile Sperm		Progressive Sperm	
		Count	(%)	Count	(%)
2001	1036	1018	98	776	75
2002	454	426	94	348	77
2003	739	727	98	574	78
2004	936	915	98	623	67
2005	907	889	98	664	73
2006	1130	1123	99	860	76
2007	429	411	96	323	75
2008	1165	1124	96	769	66
2009	1902	1883	99	1340	70
2010	1059	1018	96	735	69
Mean	976	953	97	701	73
SD	417	416	2	286	4
N	10	10	10	10	10

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 23

(b) (4)

Individual Sperm Motility Data - Main Males
(From the Epididymis)

Group 3: 1000 mg/kg/day

Male Number	Total Number of Sperm	Motile Sperm		Progressive Sperm	
		Count	(%)	Count	(%)
3001	1343	1315	98	946	70
3002	466	443	95	348	75
3003	807	792	98	500	62
3004	1450	1439	99	1079	74
3005	1270	1244	98	931	73
3006	992	981	99	752	76
3007	950	940	99	758	80
3008	604	591	98	440	73
3009	1350	1333	99	988	73
3010	288	272	94	206	72
Mean	952	935	98	695	73
SD	406	405	2	302	5
N	10	10	10	10	10

Appendix 23

(b) (4)

Individual Sperm Motility Data - Main Males
(From the Epididymis)

Group 4: 2000 mg/kg/day

Male Number	Total Number of Sperm	Motile Sperm		Progressive Sperm	
		Count	(%)	Count	(%)
4001	21 E	0 E	0 E	0 E	0 E
4002	1786	1770	99	1263	71
4003	697	689	99	554	79
4004	1250	1238	99	903	72
4005	1194	1172	98	714	60
4006	1648	1631	99	1137	69
4007	967	960	99	737	76
4008	1652	1617	98	1114	67
4009	1682	1661	99	1192	71
4010	1180	1152	98	828	70
Mean	1340	1321	99	938	71
SD	373	369	1	248	6
N	9	9	9	9	9

E: Excluded.

Appendix 23

(b) (4)

Individual Sperm Counts - Main Males
(From the Testis)

Group 1: 0 mg/kg/day

Male Number	Testis Weight (g)	Millions / Gram Testis
1001	1.934	125.2
1002	1.976	36.0
1003	1.653	112.8
1004	1.970	53.8
1005	1.920	139.6
1006	1.907	110.5
1007	1.593	100.4
1008	2.074	115.9
1009	1.794	116.5
1010	1.871	116.6
Mean	1.869	102.7
SD	0.149	32.4
N	10	10

Appendix 23

(b) (4)

Individual Sperm Counts - Main Males
(From the Testis)

Group 2: 500 mg/kg/day

Male Number	Testis Weight (g)	Millions / Gram Testis
2001	1.663	143.4
2002	1.799	90.8
2003	2.015	116.5
2004	1.821	109.7
2005	1.950	197.2
2006	1.940	55.8
2007	1.504	115.8
2008	1.920	129.0
2009	1.949	88.5
2010	1.562	98.6
Mean	1.812	114.5
SD	0.179	37.8
N	10	10

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 23

(b) (4)

Individual Sperm Counts - Main Males
(From the Testis)

Group 3: 1000 mg/kg/day

Male Number	Testis Weight (g)	Millions / Gram Testis
3001	1.896	97.5
3002	1.783	164.9
3003	1.935	60.9
3004	2.013	90.3
3005	1.667	143.1
3006	1.889	126.3
3007	1.794	138.1
3008	1.644	129.3
3009	1.827	131.6
3010	1.713	117.7
Mean	1.816	120.0
SD	0.120	29.9
N	10	10

Appendix 23

(b) (4)

Individual Sperm Counts - Main Males
(From the Testis)

Group 4: 2000 mg/kg/day

Male Number	Testis Weight (g)	Millions / Gram Testis
4001	0.226 E	32.7 E
4002	1.755	149.6
4003	1.752	72.6
4004	1.551	126.4
4005	1.710	113.5
4006	1.567	198.2
4007	1.839	118.6
4008	1.654	129.7
4009	1.814	127.4
4010	1.631	125.8
Mean	1.697	129.1
SD	0.103	33.1
N	9	9

E: Excluded.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 23

(b) (4)

Individual Sperm Counts - Main Males
(From the Cauda Epididymis)

Group 1: 0 mg/kg/day

Male Number	Cauda Epididymis Weight (g)	Millions / Gram Cauda Epididymis
1001	0.287	287.5
1002	0.281	336.2
1003	0.254	429.7
1004	0.263	362.1
1005	0.279	417.7
1006	0.284	489.0
1007	0.294	748.2
1008	0.285	434.5
1009	0.265	407.0
1010	0.243	448.5
Mean	0.273	436.0
SD	0.016	124.3
N	10	10

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 23

(b) (4)

Individual Sperm Counts - Main Males
(From the Cauda Epididymis)

Group 2: 500 mg/kg/day

Male Number	Cauda Epididymis Weight (g)	Millions / Gram Cauda Epididymis
2001	0.255	420.2
2002	0.284	489.0
2003	0.284	464.4
2004	0.267	320.6
2005	0.315	225.8
2006	0.271	283.9
2007	0.241	626.1
2008	0.293	242.4
2009	0.285	385.6
2010	0.253	301.0
Mean	0.275	375.9
SD	0.022	125.9
N	10	10

Appendix 23

(b) (4)

Individual Sperm Counts - Main Males
(From the Cauda Epididymis)

Group 3: 1000 mg/kg/day

Male Number	Cauda Epididymis Weight (g)	Millions / Gram Cauda Epididymis
3001	0.288	333.7
3002	0.255	349.2
3003	0.332	397.3
3004	0.287	402.2
3005	0.229	699.4
3006	0.295	677.6
3007	0.266	275.4
3008	0.276	526.5
3009	0.253	410.2
3010	0.255	273.3
Mean	0.274	434.5
SD	0.029	152.6
N	10	10

Appendix 23

(b) (4)

Individual Sperm Counts - Main Males
(From the Cauda Epididymis)

Group 4: 2000 mg/kg/day

Male Number	Cauda Epididymis Weight (g)	Millions / Gram Cauda Epididymis
4001	0.1324 E	10.5 E
4002	0.300	449.9
4003	0.272	317.8
4004	0.275	474.7
4005	0.258	361.2
4006	0.248	329.8
4007	0.248	431.6
4008	0.268	571.2
4009	0.254	464.3
4010	0.254	393.9
Mean	0.264	421.6
SD	0.017	80.3
N	9	9

E: Excluded.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 23

(b) (4)

Individual Sperm Motility Data - Recovery Males
(From the Epididymis)

Group 1: 0 mg/kg/day

Male Number	Total Number of Sperm	Motile Sperm Count	Motile Sperm (%)	Progressive Sperm Count	Progressive Sperm (%)
1011	1843	1759	95	1194	65
1012	1651	1559	94	1044	63
1013	1168	1113	95	815	70
1014	755	708	94	541	72
1015	1299	1269	98	961	74
Mean	1343	1282	95	911	69
SD	425	407	1	248	5
N	5	5	5	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 23

(b) (4)

Individual Sperm Motility Data - Recovery Males
(From the Epididymis)

Group 4: 2000 mg/kg/day

Male Number	Total Number of Sperm	Motile Sperm		Progressive Sperm	
		Count	(%)	Count	(%)
4011	566	544	96	442	78
4012	321	289	90	240	75
4013	382	343	90	274	72
4014	899	878	98	695	77
4015	1318	1263	96	919	70
Mean	697	663	94	514	74
SD	414	407	4	289	4
N	5	5	5	5	5

Appendix 23

(b) (4)

Individual Sperm Counts - Recovery Males
(From the Testis)

Group 1: 0 mg/kg/day

Male Number	Testis Weight (g)	Millions / Gram Testis
1011	2.023	143.5
1012	1.985	119.2
1013	1.865	100.0
1014	2.217	73.9
1015	2.107	57.5
Mean	2.039	98.8
SD	0.132	34.4
N	5	5

Appendix 23

(b) (4)

Individual Sperm Counts - Recovery Males
(From the Testis)

Group 4: 2000 mg/kg/day

Male Number	Testis Weight (g)	Millions / Gram Testis
4011	1.744	265.1
4012	1.714	78.2
4013	1.882	111.0
4014	2.115	70.4
4015	1.668	63.7
Mean	1.825	117.7
SD	0.181	84.4
N	5	5

Appendix 23

(b) (4)

Individual Sperm Counts - Recovery Males
(From the Cauda Epididymis)

Group 1: 0 mg/kg/day

Male Number	Cauda Epididymis Weight (g)	Millions / Gram Cauda Epididymis
1011	0.400	420.0
1012	0.366	535.8
1013	0.341	390.0
1014	0.335	284.3
1015	0.316	325.3
Mean	0.351	391.1
SD	0.033	96.8
N	5	5

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 23

(b) (4)

Individual Sperm Counts - Recovery Males
(From the Cauda Epididymis)

Group 4: 2000 mg/kg/day

Male Number	Cauda Epididymis Weight (g)	Millions / Gram Cauda Epididymis
4011	0.302	547.6
4012	0.285	680.3
4013	0.293	514.4
4014	0.345	440.5
4015	0.298	322.5
Mean	0.305	501.1
SD	0.023	132.3
N	5	5

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 24

24-Feb-2023 08:42:19

Individual Sperm Morphology Evaluation: Main Males

(b) (4)

Sex: Male Day: 91 Relative to Start Date

0 mg/kg /day Group 1	Normal Sperm	Abnormal Head(s)	Detached Head	Abnormal Midpiece	Abnormal Tail(s)	Coiled Tail	Abnormal Sperm Combo
1001	183	1	1	0	1	14	0
1002	181	0	0	1	2	16	0
1003	191	1	1	0	0	7	0
1004	160	0	0	0	2	37	1 [a]
1005	179	0	1	0	1	19	0
Mean	178.8	0.4	0.6	0.2	1.2	18.6	0.2
SD	11.5	0.5	0.5	0.4	0.8	11.2	0.4
N	5	5	5	5	5	5	5

[a] [RC:abnormal head, abnormal neck and/or abnormal tail]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 24

24-Feb-2023 08:42:19

Individual Sperm Morphology Evaluation: Main Males

(b) (4)

Sex: Male Day: 91 Relative to Start Date

2000 mg/kg /day Group 4	Normal Sperm	Abnormal Head(s)	Detached Head	Abnormal Midpiece	Abnormal Tail(s)	Coiled Tail	Abnormal Sperm Combo
4001	6 E[a]	4 E[b]	0 E[b]	0 E[b]	2 E[b]	0 E[b]	5 E[c]
4002	170	0	0	0	3	27	0
4003	177	1	0	1	2	19	0
4004	172	1	0	0	1	26	0
4005	176	1	0	1	1	21	0
Mean	173.8	0.8	0.0	0.5	1.8	23.3	0.0
SD	3.3	0.5	0.0	0.6	1.0	3.9	0.0
N	4	4	4	4	4	4	4

E = Exclude

[a] [RC:number of spermatozoa evaluated on both slides < to 200, FC:gross lesion not related to test item]

[b] [FC:gross lesion not related to test item]

[c] [RC:abnormal head, abnormal neck and/or abnormal tail, FC:gross lesion not related to test item]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 24

24-Feb-2023 08:42:19

Individual Sperm Morphology Evaluation: Main Males

(b) (4)

Sex: Male Day: 92 Relative to Start Date

0 mg/kg /day Group 1	Normal Sperm	Abnormal Head(s)	Detached Head	Abnormal Midpiece	Abnormal Tail(s)	Coiled Tail	Abnormal Sperm Combo
1006	184	0	0	0	0	16	0
1007	179	1	1	0	0	18	1 [a]
1008	173	0	0	0	8	19	0
1009	181	1	0	0	0	18	0
1010	184	0	2	1	1	12	0
Mean	180.2	0.4	0.6	0.2	1.8	16.6	0.2
SD	4.5	0.5	0.9	0.4	3.5	2.8	0.4
N	5	5	5	5	5	5	5

[a] [RC:abnormal head, abnormal neck and/or abnormal tail]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 24

24-Feb-2023 08:42:19

Individual Sperm Morphology Evaluation: Main Males

(b) (4)

Sex: Male Day: 92 Relative to Start Date

2000 mg/kg /day Group 4	Normal Sperm	Abnormal Head(s)	Detached Head	Abnormal Midpiece	Abnormal Tail(s)	Coiled Tail	Abnormal Sperm Combo
4006	176	0	2	0	1	21	0
4007	167	0	3	0	2	28	0
4008	177	0	1	0	0	21	1 [a]
4009	192	0	0	0	0	8	0
4010	178	3	1	0	1	17	0
Mean	178.0	0.6	1.4	0.0	0.8	19.0	0.2
SD	9.0	1.3	1.1	0.0	0.8	7.3	0.4
N	5	5	5	5	5	5	5

[a] [RC:abnormal head, abnormal neck and/or abnormal tail]

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 24

24-Feb-2023 08:42:18

Individual Sperm Morphology Evaluation: Recovery Males

(b) (4)

Sex: Male Day: 120 Relative to Start Date

0 mg/kg /day Group 1	Normal Sperm	Abnormal Head(s)	Detached Head	Abnormal Midpiece	Abnormal Tail(s)	Coiled Tail	Abnormal Sperm Combo
1011	175	0	2	0	0	23	0
1012	173	0	0	0	0	27	0
1013	164	0	2	1	3	30	0
1014	175	0	1	1	0	23	0
1015	167	0	3	1	1	28	0
Mean	170.8	0.0	1.6	0.6	0.8	26.2	0.0
SD	5.0	0.0	1.1	0.5	1.3	3.1	0.0
N	5	5	5	5	5	5	5

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

Appendix 24

24-Feb-2023 08:42:18

Individual Sperm Morphology Evaluation: Recovery Males

(b) (4)

Sex: Male Day: 120 Relative to Start Date

2000 mg/kg /day Group 4	Normal Sperm	Abnormal Head(s)	Detached Head	Abnormal Midpiece	Abnormal Tail(s)	Coiled Tail	Abnormal Sperm Combo
4011	175	0	1	0	1	23	0
4012	168	1	2	1	1	26	1 [a]
4013	176	1	0	0	3	20	0
4014	164	1	1	0	1	33	0
4015	172	0	1	1	1	25	0
Mean	171.0	0.6	1.0	0.4	1.4	25.4	0.2
SD	5.0	0.5	0.7	0.5	0.9	4.8	0.4
N	5	5	5	5	5	5	5

[a] [RC:abnormal head, abnormal neck and/or abnormal tail]

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 25

Historical Control Data for Han Wistar Rat Date: March 2022

Supplier: (b) (4)

Hematology

Approximate Age: 18 to 25 weeks

Parameter and Unit		N	Mean	Median	SD	Range (Central 95%)		Min	Max
Basophils Percent	M	123	0.230	0.200	0.120	0.100	0.500	0.000	0.600
(%)	F	117	0.300	0.300	0.220	0.000	0.800	0.000	1.20
Basophils (SI)	M	123	0.015	0.010	0.010	0.000	0.030	0.000	0.050
(10^9/L)	F	117	0.01	0.010	0.010	0.000	0.030	0.000	0.050
Eosinophils Percent	M	123	2.07	1.80	1.19	0.800	5.10	0.600	8.70
(%)	F	117	1.99	1.90	0.920	0.800	4.70	0.700	5.00
Eosinophils (SI)	M	123	0.124	0.100	0.070	0.050	0.300	0.040	0.490
(10^9/L)	F	117	0.068	0.060	0.040	0.030	0.160	0.020	0.240
Hematocrit (SI)	M	123	0.486	0.486	0.030	0.440	0.530	0.399	0.540
(L/L)	F	117	0.463	0.459	0.020	0.430	0.510	0.419	0.520
Hemoglobin (SI)	M	123	157	157	6.50	143	167	132	170
(g/L)	F	117	149	149	5.20	140	159	138	164
Large Unstained Cells Percent	M	123	0.420	0.400	0.230	0.100	1.00	0.100	1.20
(%)	F	114	0.520	0.500	0.220	0.200	1.00	0.000	1.10
Large Unstained Cells (SI)	M	123	0.028	0.020	0.020	0.000	0.090	0.000	0.150
(10^9/L)	F	114	0.018	0.020	0.010	0.000	0.040	0.000	0.050
Lymphocytes Percent	M	123	71.8	73.8	9.67	47.2	84.1	29.0	86.5
(%)	F	117	74.5	76.0	7.62	57.3	85.3	52.3	88.7
Lymphocytes (SI)	M	123	4.38	4.31	1.15	2.29	6.59	1.40	7.57
(10^9/L)	F	117	2.63	2.57	0.870	1.30	4.40	1.06	6.02
Mean Corpuscular Hemoglobin Concentration (SI)	M	123	323	321	11.1	305	345	302	353
(g/L)	F	117	323	323	8.30	304	336	303	338
Mean Corpuscular Hemoglobin	M	123	17.8	17.7	0.830	16.4	19.5	15.6	21.1
(pg)	F	117	18.8	18.8	0.630	17.7	20.3	17.4	20.5
Mean Corpuscular Volume	M	123	55.1	54.9	2.26	51.2	60.0	48.9	62.8
(fL)	F	117	58.2	57.8	2.02	54.6	63.1	54.2	64.0
Monocytes Percent	M	123	2.80	2.60	0.960	1.30	5.20	1.30	5.60
(%)	F	117	2.62	2.50	1.00	1.10	5.00	1.00	7.00
Monocytes (SI)	M	123	0.177	0.150	0.100	0.070	0.440	0.040	0.600
(10^9/L)	F	117	0.093	0.090	0.050	0.030	0.230	0.020	0.330
Neutrophils Percent	M	123	22.7	20.8	9.00	12.3	47.0	9.80	64.0
(%)	F	117	20.1	19.8	7.15	9.70	36.5	7.00	41.3
Neutrophils (SI)	M	123	1.44	1.18	1.05	0.700	3.51	0.580	9.44
(10^9/L)	F	117	0.695	0.600	0.330	0.290	1.34	0.220	2.34

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 25

Historical Control Data for Han Wistar Rat Date: March 2022

Supplier: (b) (4)

Hematology

Approximate Age: 18 to 25 weeks

Parameter and Unit		N	Mean	Median	SD	Range (Central 95%)		Min	Max
Platelet Count (SI)	M	122	876	865	124	673	1.12	646	1342
(10^9/L)	F	114	862	868	115	635	1.06	554	1211
Red Blood Cell Count (SI)	M	123	8.83	8.86	0.470	7.97	9.69	7.37	10.1
(10^12/L)	F	117	7.96	7.96	0.350	7.33	8.63	7.12	9.08
Reticulocytes	M	123	197	195	29.1	139	259	131	301
(10^9/L)	F	117	220	223	45.5	135	287	78.8	419
Reticulocytes Percent	M	123	2.24	2.20	0.370	1.60	3.10	1.50	3.50
(%)	F	117	2.78	2.80	0.620	1.70	3.80	1.00	5.30
White Blood Cell Count (SI)	M	123	6.17	5.89	1.83	3.90	9.52	2.21	17.9
(10^9/L)	F	117	3.51	3.30	1.06	1.90	5.60	1.52	7.11

NC: Not calculated.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 25

Historical Control Data for Han Wistar Rat Date: March 2022

Supplier: (b) (4)

Coagulation

Approximate Age: 18 to 25 weeks

Parameter and Unit		N	Mean	Median	SD	Range (Central 95%)		Min	Max
Activated Partial Thromboplastin Time	M	120	15.9	16.3	1.32	13.0	17.8	11.6	18.8
(s)	F	114	15.7	15.8	1.32	13.0	17.8	11.8	18.4
Fibrinogen (SI)	M	100	2.60	2.52	0.620	1.88	4.12	1.39	5.93
(g/L)	F	94	1.80	1.77	0.300	1.45	2.31	0.830	3.20
Prothrombin Time	M	120	19.9	19.9	1.79	16.7	23.2	16.0	24.0
(s)	F	114	19.8	19.6	1.45	17.3	22.6	16.2	23.4

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 25

Historical Control Data for Han Wistar Rat Date: March 2022

Supplier: (b) (4)

Biochemistry

Approximate Age: 18 to 25 weeks

Parameter and Unit		N	Mean	Median	SD	Range (Central 95%)		Min	Max
Alanine Aminotransferase	M	126	27.6	25.0	10.0	17.0	55.0	14.0	74.0
(U/L)	F	119	19.0	19.0	4.50	13.0	30.0	11.0	35.0
Albumin/Globulin Ratio	M	126	1.08	1.10	0.100	0.900	1.30	0.700	1.30
(ratio)	F	119	1.23	1.20	0.080	1.10	1.40	1.00	1.40
Albumin (SI)	M	126	33.7	33.9	1.52	30.6	35.6	25.7	35.9
(g/L)	F	119	37.1	37.0	2.00	33.3	41.3	32.5	41.8
Alkaline Phosphatase	M	126	79.2	76.0	20.6	51.0	128	40.0	170
(U/L)	F	119	38.5	38.0	12.9	20.0	68.0	17.0	77.0
Aspartate Aminotransferase	M	126	94.2	88.0	23.0	64.0	141	61.0	160
(U/L)	F	119	82.8	80.0	15.5	59.0	114	53.0	140
Bile Acids	M	25	12.8	7.70	12.5	NC	NC	3.10	52.9
(umol/L)	F	25	18.2	14.4	13.4	NC	NC	6.00	57.4
Calcium (SI)	M	126	2.56	2.56	0.070	2.42	2.69	2.36	2.72
(mmol/L)	F	119	2.58	2.59	0.080	2.43	2.78	2.42	2.82
Chloride (SI)	M	126	104	104	1.50	101	106	99.0	107
(mmol/L)	F	119	104	105	1.70	101	107	97.0	108
Cholesterol (SI)	M	126	1.55	1.50	0.320	1.06	2.26	0.960	3.01
(mmol/L)	F	119	1.65	1.60	0.400	1.05	2.67	0.800	3.04
Creatinine (SI)	M	126	42.1	42.0	3.70	36.0	49.0	35.0	56.0
(umol/L)	F	119	49.0	48.0	6.20	42.0	60.0	39.0	80.0
Globulin (SI)	M	126	31.4	31.3	2.50	27.4	36.6	26.3	42.8
(g/L)	F	119	30.2	30.3	2.07	26.6	34.0	24.8	35.4
Glucose (SI)	M	126	8.41	8.37	1.62	5.67	11.7	4.76	12.7
(mmol/L)	F	119	6.77	6.58	1.31	4.72	9.60	4.21	12.3
HDL Cholesterol (SI)	M	70	0.494	0.480	0.080	0.360	0.650	0.350	0.730
(mmol/L)	F	70	0.559	0.540	0.120	0.370	0.860	0.330	0.980
LDL Cholesterol (SI)	M	70	0.133	0.120	0.050	0.070	0.220	0.060	0.340
(mmol/L)	F	70	0.124	0.110	0.040	0.070	0.240	0.060	0.260

NC: Not calculated.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 25

Historical Control Data for Han Wistar Rat Date: March 2022

Supplier: (b) (4)

Biochemistry

Approximate Age: 18 to 25 weeks

Parameter and Unit		N	Mean	Median	SD	Range (Central 95%)		Min	Max
Phosphorus (SI)	M	126	1.87	1.83	0.250	1.47	2.41	1.38	2.54
(mmol/L)	F	119	1.70	1.74	0.280	1.07	2.22	0.940	2.30
Potassium (SI)	M	125	4.87	4.80	0.560	4.20	6.40	3.90	7.30
(mmol/L)	F	119	4.11	4.00	0.480	3.60	5.50	3.30	6.90
Sodium (SI)	M	126	142	142	1.20	140	145	139	145
(mmol/L)	F	119	142	142	1.40	140	144	139	145
Total Bilirubin (SI)	M	125	2.92	2.90	0.530	2.10	3.90	0.300	5.00
(umol/L)	F	119	3.03	3.00	0.660	1.10	4.20	0.100	4.20
Total Protein (SI)	M	126	65.1	64.9	2.64	60.5	70.1	59.2	76.0
(g/L)	F	119	67.3	67.2	3.46	61.3	74.6	58.4	76.5
Triglycerides (SI)	M	126	1.14	1.00	0.530	0.420	2.47	0.370	3.40
(mmol/L)	F	119	0.544	0.500	0.210	0.320	0.950	0.290	1.94
Urea (SI)	M	126	5.30	5.20	0.810	4.00	7.10	4.00	8.10
(mmol/L)	F	119	6.96	6.90	1.10	5.30	8.90	4.60	14.3

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 25

Historical Control Data for Han Wistar Rat Date: March 2022

Supplier: (b) (4)

Urinalysis

Approximate Age: 18 to 25 weeks

Parameter and Unit		N	Mean	Median	SD	Range (Central 95%)		Min	Max
Urine Osmolality	M	26	933	926	172	NC	NC	624	1392
(mOsmol/kg)	F	25	1121	1060	316	NC	NC	718	2326
Urine pH	M	111	8.30	8.50	0.630	7.00	9.00	7.00	9.00
	F	104	7.11	7.00	0.830	6.00	8.70	5.50	9.00
Urine Specific Gravity	M	111	1.02	1.02	0.010	1.01	1.04	1.01	1.05
	F	104	1.02	1.02	0.010	1.01	1.04	1.01	1.06

NC: Not calculated.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 25

Historical Control Data for Han Wistar Rat Date: March 2022

Supplier: (b) (4)

Biomarker

Approximate Age: 18 to 25 weeks

Parameter and Unit		N	Mean	Median	SD	Range (Central 95%)		Min	Max
Thyroid Stimulating Hormone	M	15	0.213	0.179	0.120	NC	NC	0.042	0.459
(mU/L)	F	15	0.080	0.068	0.060	NC	NC	0.014	0.224
Thyroxine	M	15	46.2	48.1	8.70	NC	NC	27.0	55.3
(ng/mL)	F	15	27.0	25.8	8.13	NC	NC	15.6	39.1
Triiodothyronine, Total	M	15	0.681	0.650	0.120	NC	NC	0.540	0.940
(ng/mL)	F	15	0.784	0.770	0.140	NC	NC	0.600	1.07

NC: Not calculated.

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 26

(b) (4)

HORMONE MEASUREMENT PHASE REPORT

Determination of Thyroxine (T4), Triiodothyronine (T3) and Thyroid-Stimulating Hormone (TSH) in rat serum samples with ELISA

Test Facility Study No. (b) (4)

Sponsor Reference No. (b) (4)

Test Site Study Code: (b) (4)

90-Day Repeated Dose Toxicity Study of TRP Pro by the Oral (gavage) Route in the Wistar Han IGS Rat with a 4-week Recovery Period

(b) (4) **Study**

Principal Investigator: (b)(6)

SPONSOR:
CJ CheilJedang Corporation
55-42 Beongil Gwanggyo-ro, Yeongtong-gu
Suwon-si
16495 Gyeonggi-do
Republic of Korea

(b) (4), (b) (6)

TEST SITE:
(b) (4), (b) (6)

Appendix 26

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Appendix 26

STATEMENT OF THE PRINCIPAL INVESTIGATOR

This phase has been performed in accordance with the Study Plan and its amendments and the Principles of Good Laboratory Practice (Hungarian GLP Regulations of 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98)17.).

I the undersigned declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study. By virtue of my dated signature, I accept the responsibility for the validity of the data.

(b)(6)

21 August 2023

Principal Investigator Date

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 26

STATEMENT OF THE TEST SITE MANAGEMENT

According to the conditions of research and development assignment between (b) (4) (as Test Facility) and (b) (4) as Test Site), the phase titled " Determination of Thyroxine (T4), Triiodothyronine (T3) and Thyroid-Stimulating Hormone (TSH) in rat serum samples with ELISA " has been performed in compliance with the Study Plan and its Amendments and the Principles of Good Laboratory Practice.

(b)(6)

General Manager

21 August 2023

Date

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 26

TEST SITE QUALITY ASSURRANCE STATEMENT

Test Site Phase Code: (b) (4)
Testing Facility Study No. (b) (4)
Phase Title: Determination of Thyroxine (T4), Triiodothyronine (T3) and Thyroid-Stimulating Hormone (TSH) in rat serum samples with ELISA
Test Item: TRP Pro

This Phase has been audited by Quality Assurance in accordance with the applicable Good Laboratory Practice regulations.

All inspections, data reviews and the report audit were reported in written form to the Principal Investigator and Test Site Management; and the copies of the report were available to the Study Director, Test Facility Management and Test Facility QAU. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to		
		Test Site Management	Principal Investigator	Test Facility
21 October 2022	Study Plan Amendment 01	21 October 2022	21 October 2022	21 October 2022
28 March 2023	Study Plan Amendment 04	28 March 2023	28 March 2023	28 March 2023
16-27 March 2023/08 May 2023	Hormone analysis	27 March 2023/08 May 2023	27 March 2023/08 May 2023	NA
08-11 May 2023	Draft Phase Report and Raw Data	11 May 2023	11 May 2023	11 May 2023
18 August 2023	Final Phase Report	18 August 2023	18 August 2023	18 August 2023

N/A: these audits were not reported to the Test Facility because they were process based inspections.

In addition to the above-mentioned audits, (which may include study specific inspections and/or relevant process-based inspections) routine facility inspections were also conducted.

The Final Phase Report reflects the raw data and accurately and completely describes the methods and procedures of the study.

(b) (6) _____ 21 August 2023
Date

Appendix 26

1. OBJECTIVE

The objective of this measurement was to determine the concentrations of Thyroxine (T4), Triiodothyronine (T3) and Thyroid-Stimulating Hormone (TSH) from rat serum samples collected during the -in life phase of the study.

After reception of study serum samples, all the measurements were performed within 87 days. Samples were stored at -80±10°C until the analysis.

Methods which were used to conduct the analysis, were validated methods (validation study codes: 20/044-409PV, 20/045-409PV and 20/271-409PV) and considered to be robust and suitable for analysis of thyroid hormone measurements of rat samples.

2. SCHEDULE

Start of the measurements: 28 February 2023

End of the measurements: 13 April 2023

Draft Phase Report (QAed): 16 August 2023

Final Phase Report: 21 August 2023

3. SPONSOR

Role	Name	Contact Information
Sponsor Study Monitor/Representative Name	(b)(6)	Address as cited for Sponsor Tel: +82 31 8099 1548 E-mail: (b)(6)

4. RESPONSIBLE PERSONNEL

Role/Phase	Quality Assurance Unit	Name	Contact Information
Study Director			(b) (4), (b)(6)
Alternative Contact			
Test Facility Management			
Test Facility QAU/Lead QA			
Ophthalmology			(b) (4), (b)(6)
Safety Pharmacologist			

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

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Role/Phase	Quality Assurance Unit	Name	Contact Information
Study Pathologist	(b) (4), (b)(6)		
Principal Investigators (PI)			
T3, T4, TSH hormone measurement (Phase No. 21/300-430AN)[a]	(b) (4), (b)(6)		
Test Site Management			
Test Site QAU			

[a]: Test Site selected by the Study Sponsor in agreement with the Study Director.

Note: Other trained, competent personnel worked on the study (as documented in the raw data).

5. SAMPLE STORAGE

Blood samples were collected and processed as specified in the Study Plan.

Study serum samples were stored at -80±10°C until the date of measurements. The maximum time from blood collection to analysis was 87 days.

The maximum period of storage under frozen conditions that has been validated is 322 days for T4, 142 days T3 hormones, and 132 days for TSH.

6. ELISA KITS AND OTHER MATERIALS

T4 ELISA and T3 ELISA kits were purchased from (b) (4) and TSH ELISA kits from (b) (4)

Each kit (T4 and T3) contained a specific plate (96 well), calibration standards, wash buffer, substrate, stop solution, conjugate solution and C diluent.

TSH kits contained a TSH specific plate (96 well), master calibrator (lyophilized), enzyme conjugate, substrate solution, stop solution, wash solution (10x concentrated) and Calibrator/Sample diluent.

Distilled water was used to prepare the washing solution and to prime the sample probe (in case of T3 and T4) and to prepare the standard master solution in case of TSH. All reagents were used fresh. The ELISA kits were stored refrigerated and used according to the manufacturer's instruction within the expiry date.

Blood samples for thyroid hormone analysis were collected into tubes containing clotting activator to obtain serum.

Details of the ELISA kits, distilled water and blood collection tubes are given in **Table 1**.

7. METHODS FOR DETERMINE THYROID HORMONE LEVELS

7.1. Thyroxine (T4)

The bioanalytical method for the determination of T4 was a competitive immunoassay. Wells of a microplate were coated with an antibody specific for T4. An enzyme-T4 horseradish peroxidase-labelled conjugate was added and the reactants were mixed. A competitive reaction occurred between the enzyme-T4 conjugate and the T4 (from the rat samples) for the limited amount of antibody immobilized on the surface of the well. After the completion of the required incubation period, the antibody-bound fraction of the enzyme-T4 conjugate was separated from the unbound enzyme-T4 conjugate via a wash step. A chromogenic substrate, TMB (3,3',5,5'-Tetra-Methyl-Benzidine), was added to all wells. The substrate was converted to a coloured end product (blue) by the fixed enzyme. Enzyme reaction was stopped after a given period of time by dispensing of sulphuric acid as stop solution (change from blue to yellow), and the absorbance was measured at 450 nm. The colour intensity was proportional to the amount of the enzyme-T4 conjugate bound in the initial step, which was inversely proportional to the amount of T4 coming from the rat serum samples.

7.2. Triiodothyronine (T3)

The bioanalytical method for the determination of T3 was a competitive immunoassay. A competitive reaction occurred between the enzyme-T3 horseradish peroxidase-labelled conjugate and the T3 (from the rat samples) for the limited amount of antibody immobilized on the surface of the well. After the completion of the required incubation period, the antibody-bound fraction of the enzyme-T3 conjugate was separated from the unbound enzyme-T3 conjugate via a wash step. A chromogenic substrate TMB (3,3',5,5'-Tetra-Methyl-Benzidine) solution was then added to the wells. The substrate was converted to a coloured end product (blue) by the fixed enzyme. Enzyme reaction was stopped after a given period of time by dispensing of sulphuric acid as stop solution (change from blue to yellow), and the absorbance was measured at 450 nm. The colour intensity was proportional to the amount of the enzyme-T3 conjugate bound in the initial step, which was inversely proportional to the amount of T3 coming from the rat serum samples.

7.3. Thyroid-Stimulating Hormone (TSH)

The test is an enzyme-linked immunosorbent assay (ELISA) in the microplate format, designed for the quantitative measurement of TSH in rat serum. The microplate is coated with a monoclonal antibody specific for TSH. Calibrators, QC samples and study samples were pipetted into the antibody coated microplate. Afterwards, a polyclonal horseradish peroxidase-labelled antibody was added. During a 16-24 hours incubation at 4-8°C sandwich complexes consisting of the two antibodies and the rat TSH was formed. Non-reactive components were removed by a washing step. A chromogenic substrate, TMB (3,3',5,5'-Tetra-Methyl-Benzidine), was added to all wells. During a 30 minutes incubation, the substrate was converted to a coloured end product (blue) by the fixed enzyme. Enzyme reaction was stopped by dispensing of hydrochloric acid as stop solution (change from blue to yellow). The colour intensity was direct proportional to the concentration of rat TSH present in the sample. The optical density of the colour solution was measured with a microplate reader at 450 nm using 630 nm as differential wavelength.

8. PREPARATION OF THE CALIBRATION STANDARDS

8.1. T4 analysis

(b) (4)

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9. PREPARATION OF QUALITY CONTROL (QC) SAMPLES

9.1. T4 analysis

(b) (4)

10.1. T4 hormone analysis

For measurements of T4 each ELISA plate consisted of:

- Blank samples (zero calibrator – supplied in the kit – was used as blank)
- Six calibration standards from 0 µg/dL up to 25 µg/dL T4
- Two Quality control (QC) samples
- Study samples (individual samples)

Blank and QC samples were assayed in triplicate, and calibrators in duplicate. Study samples were assayed in duplicate, except of sample of 2001, as it was measured in a single well, due to insufficient sample volume.

10.2. T3 hormone analysis

For measurements of T3 each ELISA plate consisted of:

- Blank samples (zero calibrator – supplied in the kit – was used as blank)
- Six calibration standards from 0 ng/mL up to 7.5 ng/mL T3
- Two Quality control (QC) samples
- Study samples (individual samples)

Blank and QC samples were assayed in triplicate, calibrators and study samples were assayed in duplicate.

10.3. TSH hormone analysis

For measurements of TSH each ELISA plate consisted of:

- Eight calibration standards from 0 ng/mL up to 40 ng/mL TSH
- Three Quality control (QC) samples
- Study samples (individual samples)

Calibrators, QC samples and study samples were assayed in duplicate.

11. RESULTS OF THE ANALYSIS

11.1. Study Sample Analysis

Frozen serum from 148 adult male and 150 adult female samples were successfully analysed; 49/298 samples were <LOQ (Limit of Quantification). All the BQL (Below of Quantification Limit) values were measured during the TSH analysis. The acceptance criteria for the calibration standards and quality control samples were met on all 14 ELISA plates.

By T3 analysis, the acceptance criteria were not met in case of QC2 (Quality Control) samples - results were out of the required ±25% - on 3/5 plates due to technical error. Samples which were assayed in that plates, were re-assayed. Absorbance values of calibrators, results of QC samples and back calculated results of the calibrators used are shown in the tables but results of study samples are not included in result tables of study samples. The measurement of this samples (30 male, and 30 female samples) was repeated on the additional sixth, and seventh plate.

Results are shown in **Table 11, Table 12 and Table13.**

11.2. Calibration points

All the mean calibration standard results were ±15.60%, ±16.67% and ±23.65% of their nominal concentrations in case of T4, T3 and TSH, respectively (the criteria was within ±25%). There were eight excluded samples during the analysis, so the criteria were met (8/188) samples were excluded).

Values and means, and absorbance values of calibration points for all plates are shown in **Table 2, Table 3, Table 4 and Table 8, Table 9, Table 10.**

Standard curves of TSH analysis are shown in **Figure 1-5.**

11.3. Quality control samples

The mean QC values of valid plates were all within ±10.48%, ±25.00% and ±16.33% of their nominal concentrations in case of T4, T3 and TSH, respectively (the criteria was within ±25%). There was one excluded sample during the analysis, so the criteria were met (1/84 samples were excluded).

Results of the mean for each of the QC samples should be within ±25% of their nominal values, and valid results should be obtained for at least one out of two duplicate results for each QC level; individual results that are clearly outliers and considered to be erroneous were excluded.

Values and means of QC values for all plates are shown in **Table 5, Table 6 and Table 7.**

12. DISCUSSION AND CONCLUSION

All the mean calibration standard results were ±15.60%, ±16.67% and ±23.65% of their nominal concentrations in case of T4, T3 and TSH, respectively.

The mean QC values of valid plates were all within ±10.48%, ±25.00% and ±16.33% of their nominal concentrations in case of T4, T3 and TSH, respectively.

Acceptance criterion was that actually measured, and back calculated differences should be within ±25% for both the calibration points and for quality control samples during the measurement.

The acceptance criteria for the calibration points and quality control samples obtained during the T4, T3 and TSH measurement phase were met for a successful analysis of the study samples.

13. REGULATORY COMPLIANCE

In order to enable the results of this study phase to meet the requirements for regulatory submission and/or safety assessment, it was performed in compliance with the principles of Good Laboratory Practice Regulations as requested by the Sponsor and specified in the Hungarian Good Laboratory Practice Regulations: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities that correspond to the OECD GLP, ENV/MC/CHEM (98) 17.

These principles are consistent with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community (EMA and National Competent Authorities), the United States (EPA and FDA), and Japan (MHLW, MAFF and METI).

14. COMPUTERIZED SYSTEMS

The following computerized systems used in the study:

Critical Computerized Systems

System Name	**Description of Data Collected and/or Analysed**
Elysis Uno	Performing of T3 and T4 ELISA assays and read absorbance values of TSH assays

15. RETENTION AND DISPOSITION OF RECORDS AND SAMPLES

As demanded by the principles of Hungarian GLP and the relevant SOPs of the Test Site, all the phase related documents such as, but not limited to, all raw data, the original Final Phase Report and any amendment(s), shipping documents and correspondence, will be archived for a period of 15 years following the date on which the Final Phase Report will be issued in the Archive of the Test Site (H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1., Hungary). It is the responsibility of the Principal Investigator (PI) to notify the Study Director when the Final Phase Report is archived.

After the retention time at the Test Site has elapsed, the Test Site will contact the Study Director (on behalf of Sponsor) for instructions whether all the archived materials listed above will be offered to the Sponsor or retained for a further period (if agreed by a contract) in the Archive of the Test Site or transferred to external archiving.

All the measured results were within the acceptance criteria; therefore, the remaining samples will be disposed in a safe and proper manner, in accordance with the Study Plan.

16. DISTRIBUTION OF THE PHASE REPORT

Sponsor / Study Director:	1x PDF-file
Archive of the Test Site:	1x original, bound

Appendix 26

17. TABLES AND STANDARD CURVES

Table 1

Material	Name	Supplier	Reference number	Lot number	Expiry date	Storage condition
ELISA kit	T4 ELISA	(b) (4)	54020	22502	July 15, 2024	2-8°C
ELISA kit	T3 ELISA		54010	22501	July 28, 2024	2-8°C
ELISA kit	T3 ELISA		54010	22001	June 14, 2024	2-8°C
ELISA kit	TSH rat ELISA		DEV9977	V069	November 30, 2023	2-8°C
Distilled water	Aqua purificata		590001	2211-8352	May 4, 2023	Room temperature

Table 1- Details of the ELISA kits, distilled water

Back calculated results of T4 calibrators (µg/dL)

	Calibrators					
Sample ID	**Cal A**	**Cal B**	**Cal C**	**Cal D**	**Cal E**	**Cal F**
Theoretical concentration	0	2	5	10	15	25
	Assays					
Plate 1	0.0	1.9	5.1	9.6	12.8	25.0
	0.3*	1.9	5.3	9.9	13.1	25.0
Mean	0.00	1.90	5.20	9.75	12.95	25.00
%Diff to theoretical conc.	***NA***	***-5.00***	***4.00***	***-2.50***	***-13.67***	***0.00***
Plate 2	0.0	1.9	5.1	9.9	12.6	25.0
	0.3*	1.9	5.2	10.0	12.4	25.0
Mean	0.00	1.90	5.15	9.95	12.50	25.00
%Diff to theoretical conc.	***NA***	***-5.00***	***3.00***	***-0.50***	***-16.67***	***0.00***
Plate 3	0.0	1.9	5.1	9.8	13.4	25.0
	0.0	2.1	5.1	9.9	13.0	25.0
Mean	0.00	2.00	5.10	9.85	13.20	25.00
%Diff to theoretical conc.	***NA***	***0.00***	***2.00***	***-1.50***	***-12.00***	***0.00***
Plate 4	0.0	1.8	5.1	9.8	12.5	25.0
	0.0	2.0	5.2	10.2	13.2	25.0
Mean	0.00	1.90	5.15	10.00	12.85	25.00
%Diff to theoretical conc.	***NA***	***-5.00***	***3.00***	***0.00***	***-14.33***	***0.00***
Plate 5	0.0	1.9	5.1	10.0	13.4	25.0
	0.0	2.0	5.1	9.9	13.0	25.0
Mean	0.00	1.95	5.10	9.95	13.20	25.00
%Diff to theoretical conc.	***NA***	***-2.50***	***2.00***	***-0.50***	***-12.00***	***0.00***

* Excluded from calibration curve

Table 2 - Back calculated results of T4 calibrators (µg/dL)

Appendix 26

Back calculated results of T3 calibrators (ng/mL)

	Calibrators					
Sample ID	**Cal A**	**Cal B**	**Cal C**	**Cal D**	**Cal E**	**Cal F**
Theoretical concentration	0	0.5	1.0	2.5	5.0	7.5
			Assays			
Plate 1	0.00	0.50	1.14	2.31	4.59	7.50
	0.00	0.48	1.04	2.38	4.59	7.50
Mean	0.00	0.49	1.09	2.35	4.59	7.50
%Diff to theoretical conc.	***NA***	***-2.00***	***9.00***	***-6.20***	***-8.20***	***0.00***
Plate 2	0.00	0.47	1.02	2.31	4.48	7.50
	0.00	0.39	1.15	2.64	4.37	7.50
Mean	0.00	0.43	1.09	2.48	4.43	7.50
%Diff to theoretical conc.	***NA***	***-14.00***	***8.50***	***-1.00***	***-11.50***	***0.00***
Plate 3	0.04*	0.47	1.03	2.53	5.09	7.04
	0.00	0.48	1.05	2.37	4.80*	7.50
Mean	0.00	0.48	1.04	2.45	5.09	7.27
%Diff to theoretical conc.	***NA***	***-5.00***	***4.00***	***-2.00***	***1.80***	***-3.07***
Plate 4	0.02	0.49	1.04	2.31	4.40	7.50
	0.00	0.43	1.16	2.38	4.31	7.50
Mean	0.01	0.46	1.10	2.35	4.36	7.50
%Diff to theoretical conc.	***NA***	***-8.00***	***10.00***	***-6.20***	***-12.90***	***0.00***
Plate 5	0.00	0.43	1.06	2.62	4.41	7.50
	0.00	0.49	1.03	2.42	4.39	7.50
Mean	0.00	0.46	1.05	2.52	4.40	7.50
%Diff to theoretical conc.	***NA***	***-8.00***	***4.50***	***0.80***	***-12.00***	***0.00***
Plate 6	0.02	0.48	1.07	2.28	4.25	7.50
	0.00	0.45	1.07	2.59	4.19	7.50
Mean	0.01	0.47	1.07	2.44	4.22	7.50
%Diff to theoretical conc.	***NA***	***-7.00***	***7.00***	***-2.60***	***-15.60***	***0.00***
Plate 7	0.00	0.49	1.04	2.25	4.57	7.50
	0.00	0.48	1.17	2.25	4.15	7.50
Mean	0.00	0.49	1.11	2.25	4.36	7.50
%Diff to theoretical conc.	***NA***	***-3.00***	***10.50***	***-10.00***	***-12.80***	***0.00***

NA Not applicable

Table 3 - Back calculated results of T3 calibrators (ng/mL)

Appendix 26

Back calculated results of TSH calibrators (ng/mL)

	Calibrators							
Sample ID	**Cal 1**	**Cal 2**	**Cal 3**	**Cal 4**	**Cal 5**	**Cal 6**	**Cal 7**	**Cal 8**
Theoretical concentration	40	20	10	5	2.50	1.25	0.625	0
			Assays					
Plate 1	35.94	20.25	9.95	4.83	2.53	1.17	0.60	0.18
	44.87	19.75	6.77*	5.54	2.13	1.07	0.44	0.23
Mean	40.40	20.00	9.95	5.18	2.33	1.12	0.52	0.21
%Diff to theoretical conc.	***1.01***	***0.00***	***-0.49***	***3.67***	***-6.75***	***-10.28***	***-16.31***	***NA***
Plate 2	37.82	19.70	10.02	4.95	2.29	1.05	0.52	0.34
	42.35	20.28	7.46*	5.25	2.24	1.05	0.58	0.34
Mean	40.09	19.99	10.02	5.10	2.27	1.05	0.55	0.34
%Diff to theoretical conc.	***0.21***	***-0.05***	***0.22***	***1.98***	***-9.38***	***-16.38***	***-12.11***	***NA***
Plate 3	37.04	20.13	9.88	4.88	2.48	2.24*	0.52	0.25
	43.40	19.87	7.70*	5.75	2.05	1.04	0.45	0.32
Mean	40.22	20.00	9.88	5.31	2.27	1.04	0.48	0.29
%Diff to theoretical conc.	***0.55***	***-0.01***	***-1.23***	***6.29***	***-9.38***	***-17.05***	***-22.53***	***NA***
Plate 4	38.15	19.73	9.68	5.28	2.59	1.04	0.60	0.24
	42.00	20.27	9.74	5.80	2.17*	0.87	0.51	0.33
Mean	40.07	20.00	9.71	5.54	2.59	0.95	0.55	0.28
%Diff to theoretical conc.	***0.19***	***0.00***	***-2.90***	***10.74***	***3.63***	***-23.65***	***-11.61***	***NA***
Plate 5	38.02	19.91	10.36	5.62	2.71	1.16	0.49	0.15
	42.11	20.11	9.07	5.33	2.33*	1.16	0.49	0.15
Mean	40.06	20.01	9.72	5.47	2.71	1.16	0.49	0.15
%Diff to theoretical conc.	***0.15***	***0.07***	***-2.85***	***9.49***	***8.36***	***-7.27***	***-21.98***	***NA***

NA Not applicable

***** Excluded from standard curve calculation

Table 4 - Back calculated results of TSH calibrators (ng/mL)

Appendix 26

Back calculated results of T4 Quality Control samples (µg/dL)

	Quality control samples	
Sample ID	**QC 1**	**QC 2**
Theoretical concentration	3.5	7.5
Assays		
	3.7	7.1
Plate 1	4.1	7.1
	3.6	7.3
Mean	3.80	7.17
%Diff to theoretical conc.	***8.57***	***-4.44***
	4.0	7.4
Plate 2	3.8	7.2
	3.8	7.5
Mean	3.87	7.37
%Diff to theoretical conc.	***10.48***	***-1.78***
	3.6	7.2
Plate 3	3.6	7.3
	3.4	7.4
Mean	3.53	7.30
%Diff to theoretical conc.	***0.95***	***-2.67***
	3.8	7.5
Plate 4	3.7	7.6
	3.7	8.0
Mean	3.73	7.70
%Diff to theoretical conc.	***6.67***	***2.67***
	3.8	7.2
Plate 5	3.7	7.1
	3.6	7.4
Mean	3.70	7.23
%Diff to theoretical conc.	***5.71***	***-3.56***

Table 5 - Back calculated results of T4 Quality Control samples (µg/dL)

Appendix 26

Back calculated results of T3 Quality Control samples (ng/mL)

	Quality control samples		
Sample ID	**QC 1**	**QC 2**	QC
Theoretical concentration	0.75	2.5	1.5
Assays			
	0.79	2.24	
Plate 1	0.81	2.02	
	0.84	2.10	
Mean	0.81	2.12	
%Diff to theoretical conc.	***8.44***	***-15.20***	
	0.61	1.80	
Plate 2	0.76	1.65*	
	0.56	1.95	
Mean	0.64	1.88	
%Diff to theoretical conc.	***-14.22***	***-25.00***	
	0.73	1.81	
Plate 3	0.73	1.89	
	0.65	1.81*	
Mean	0.70	1.85	
%Diff to theoretical conc.	***-6.22***	***-26.00***	
	0.72	1.65	
Plate 4	0.70	1.57	
	0.61	1.68	
Mean	0.68	1.63	
%Diff to theoretical conc.	***-9.78***	***-34.67***	
	0.65		1.08
Plate 5	0.61		1.04
	0.64		1.01
Mean	0.63		1.04
%Diff to theoretical conc.	***-15.56***		***-30.44***
	0.74	2.26	
Plate 6	0.73	2.21	
	0.86	2.20	
Mean	0.78	2.22	
%Diff to theoretical conc.	***3.56***	***-11.07***	
	0.68	2.36	
Plate 7	0.76	2.36	
	0.74	2.30	
Mean	0.73	2.34	
%Diff to theoretical conc.	***-3.11***	***-6.40***	

* Result was excluded from calculation

Table 6 - Back calculated results of T3 Quality Control samples (ng/mL)

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Back calculated results of TSH Quality Control samples (ng/mL)

	Quality control samples		
Sample ID	**QC 1**	**QC 2**	**QC 3**
Theoretical concentration	30	3.75	1.875
	Assays		
Plate 1	29.5	3.73	1.733
	29.1	4.05	1.632
Mean	29.32	3.89	1.683
%Diff to theoretical conc.	***-2.26***	***3.76***	***-10.26***
Plate 2	31.0	3.81	1.676
	30.7	3.81	1.562
Mean	30.84	3.81	1.619
%Diff to theoretical conc.	***2.79***	***1.61***	***-13.67***
Plate 3	29.2	4.14	1.611
	30.8	3.91	1.548
Mean	29.99	4.03	1.579
%Diff to theoretical conc.	***-0.02***	***7.36***	***-15.77***
Plate 4	27.8	4.21	1.482
	26.6	3.97	1.656
Mean	27.17	4.09	1.569
%Diff to theoretical conc.	***-9.42***	***9.08***	***-16.33***
Plate 5	29.8	4.41	1.815
	31.7	4.11	1.620
Mean	30.76	4.26	1.718
%Diff to theoretical conc.	***2.55***	***13.68***	***-8.39***

Table 7 - Back calculated results of TSH Quality Control samples (ng/mL)

Absorbance values and global SD of T4 calibrators

Calibrators	**Absorbances**					
	Plate 1	**Plate 2**	**Plate 3**	**Plate 4**	**Plate 5**	**Global SD**
Cal A	2.633	2.604	2.674	2.748	2.807	0.069
	2.451*	2.412*	2.680	2.718	2.799	
Cal B	1.971	1.903	1.840	2.023	1.889	0.071
	1.966	1.901	1.774	1.972	1.859	
Cal C	1.140	1.087	1.023	1.166	1.059	0.050
	1.109	1.069	1.025	1.160	1.059	
Cal D	0.603	0.556	0.543	0.616	0.543	0.027
	0.586	0.549	0.540	0.591	0.548	
Cal E	0.460	0.437	0.405	0.489	0.408	0.026
	0.450	0.444	0.416	0.467	0.419	
Cal F	0.314	0.292	0.273	0.324	0.276	0.020
	0.314	0.279	0.275	0.315	0.273	

* Excluded from calibration curve

Table 8 - Absorbance values and global SD of T4 calibrators

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Absorbance values and global SD of T3 calibrators

Calibrators	Absorbances							Global SD
	Plate 1	Plate 2	Plate 3	Plate 4	Plate 5	Plate 6	Plate 7	
Cal A	2.050	2.005	1.927	2.081	1.851	2.136	2.234	0.141
	2.036	1.780	1.992*	2.128	1.737	2.168	2.238	
Cal B	1.585	1.520	1.524	1.581	1.453	1.633	1.667	0.052
	1.594	1.575	1.516	1.633	1.414	1.660	1.681	
Cal C	1.172	1.160	1.166	1.174	1.069	1.191	1.239	0.043
	1.228	1.090	1.152	1.110	1.085	1.191	1.163	
Cal D	0.730	0.662	0.636	0.674	0.560	0.711	0.739	0.051
	0.714	0.590	0.671	0.657	0.600	0.640	0.740	
Cal E	0.408	0.388	0.353	0.411	0.363	0.446	0.457	0.031
	0.408	0.394	0.397*	0.416	0.364	0.450	0.479	
Cal F	0.287	0.306	0.300	0.301	0.278	0.331	0.356	0.027
	0.281	0.301	0.290	0.311	0.269	0.336	0.351	

Table 9 - Absorbance values and global SD of T3 calibrators

Absorbance values and global SD of TSH calibrators

Calibrators	Absorbances					Global SD
	Plate 1	Plate 2	Plate 3	Plate 4	Plate 5	
Cal 1	1.425	1.217	1.336	1.163	1.173	0.142
	1.634	1.318	1.454	1.209	1.246	
Cal 2	0.677	0.539	0.580	0.472	0.527	0.058
	0.649	0.563	0.565	0.516	0.536	
Cal 3	0.263	0.234	0.216	0.164	0.221	0.034
	0.180*	0.175*	0.169*	0.165	0.193	
Cal 4	0.135	0.123	0.115	0.098	0.126	0.014
	0.151	0.129	0.131	0.105	0.121	
Cal 5	0.086	0.073	0.074	0.064*	0.077*	0.007
	0.078	0.072	0.067	0.059	0.071	
Cal 6	0.059	0.051	0.070*	0.046	0.053	0.004
	0.057	0.051	0.051	0.044	0.053	
Cal 7	0.048	0.042	0.043	0.041	0.043	0.002
	0.045	0.043	0.042	0.040	0.043	
Cal 8	0.040	0.039	0.039	0.037	0.038	0.001
	0.041	0.039	0.040	0.038	0.038	

* Excluded from standard curve calculation

Table 10 - Absorbance values and global SD of TSH calibrators

Appendix 26

Results of T4 measurements

Animal ID Male	T4 conc. (ng/ml)		Animal ID Female	T4 conc. (ng/ml)	
1001	46	*	**1501**	26	*
1002	53	*	**1502**	33	*
1003	54	*	**1503**	32	*
1004	44	*	**1504**	27	*
1005	45	*	**1505**	38	*
1006	45	*	**1506**	39	*
1007	45	*	**1507**	43	*
1008	46	*	**1508**	52	*
1009	37	*	**1509**	29	*
1010	39	*	**1510**	28	*
1011	47	*	**1511**	38	*
1012	47	*	**1512**	35	*
1013	46	*	**1513**	26	*
1014	40	*	**1514**	34	*
1015	41	*	**1515**	27	*
2001	60	Measured in singlicate	**2501**	22	*
2002	59	*	**2502**	31	*
2003	52	*	**2503**	31	*
2004	48	*	**2504**	40	*
2005	51	*	**2505**	21	*
2006	49	*	**2506**	42	*
2007	42	*	**2507**	35	*
2008	48	*	**2508**	47	*
2009	41	*	**2509**	37	*
2010	33	*	**2510**	39	*
3001	50	*	**3501**	39	*
3002	53	*	**3502**	33	*
3003	47	*	**3503**	25	*
3004	50	*	**3504**	31	*
3005	46	*	**3505**	27	*
3006	44	*	**3506**	43	*
3007	46	*	**3507**	41	*
3008	48	*	**3508**	45	*
3009	41	*	**3509**	28	*
3010	41	*	**3510**	37	*
4001	53	*	**4501**	39	*
4002	48	*	**4502**	33	*
4003	48	*	**4503**	28	*
4004	53	*	**4504**	32	*
4005	45	*	**4505**	24	*
4006	48	*	**4506**	54	*
4007	42	*	**4507**	46	*
4008	39	*	**4508**	40	*
4009	38	*	**4509**	43	*
4010	40	*	**4510**	31	*
4011	48	*	**4511**	33	*
4012	40	*	**4512**	33	*
4013	41	*	**4513**	39	*
4014	37	*	**4514**	29	*
4015	36	*	**4515**	33	*

* Measured in duplicate

Table 11 - Results of T4 measurements

Appendix 26

Results of T3 measurements

Animal ID Male	T3 conc. (ng/ml)		Animal ID Female	T3 conc. (ng/ml)	
1001	1.32	*	**1501**	1.26	*
1002	1.42	*	**1502**	1.50	*
1003	1.45	*	**1503**	1.41	*
1004	1.13	*	**1504**	0.71	*
1005	1.02	*	**1505**	1.07	*
1006	1.21	**	**1506**	1.03	**
1007	1.39	**	**1507**	1.22	**
1008	1.15	**	**1508**	1.48	**
1009	1.03	**	**1509**	1.03	**
1010	1.25	**	**1510**	0.74	**
1011	1.39	**	**1511**	1.11	**
1012	1.11	**	**1512**	0.85	**
1013	0.96	**	**1513**	0.99	**
1014	0.78	**	**1514**	0.95	**
1015	0.94	**	**1515**	0.87	**
2001	No sample		**2501**	1.01	*
2002	1.59	*	**2502**	1.38	*
2003	1.47	*	**2503**	1.16	*
2004	1.23	*	**2504**	1.24	*
2005	1.06	*	**2505**	0.59	*
2006	1.33	**	**2506**	1.07	**
2007	1.22	**	**2507**	1.16	**
2008	1.09	**	**2508**	1.01	**
2009	1.12	**	**2509**	0.98	**
2010	1.02	**	**2510**	0.94	**
3001	1.20	*	**3501**	1.29	*
3002	1.67	*	**3502**	1.34	*
3003	1.51	*	**3503**	1.36	*
3004	1.32	*	**3504**	0.96	*
3005	1.12	*	**3505**	0.89	*
3006	1.50	**	**3506**	1.22	**
3007	1.33	**	**3507**	1.27	**
3008	1.16	**	**3508**	1.10	**
3009	1.15	**	**3509**	0.76	**
3010	1.05	**	**3510**	1.05	**
4001	1.72	*	**4501**	1.38	*
4002	1.56	*	**4502**	1.43	*
4003	1.18	*	**4503**	1.41	*
4004	1.21	*	**4504**	1.31	*
4005	1.18	*	**4505**	0.78	*
4006	1.39	**	**4506**	1.60	**
4007	1.07	**	**4507**	1.32	**
4008	1.26	**	**4508**	1.09	**
4009	0.88	**	**4509**	1.02	**
4010	1.17	**	**4510**	0.87	**
4011	1.17	**	**4511**	0.90	**
4012	0.72	**	**4512**	1.00	**
4013	0.93	**	**4513**	0.82	**
4014	0.74	**	**4514**	0.67	**
4015	0.78	**	**4515**	0.86	**

* Measured in duplicate
** Repeated measurement, measured in duplicate

Table 12 - Results of T3 measurements

Appendix 26

Results of TSH measurements

Animal ID Male	TSH conc. (pg/ml)		Animal ID Female	TSH conc. (pg/ml)	
1001	549	BQL	**1501**	343	BQL
1002	392	BQL	**1502**	461	BQL
1003	339	BQL	**1503**	725	
1004	602	BQL	**1504**	520	BQL
1005	392	BQL	**1505**	490	BQL
1006	615	BQL	**1506**	462	BQL
1007	418	BQL	**1507**	910	
1008	582	BQL	**1508**	777	
1009	713		**1509**	417	BQL
1010	550	BQL	**1510**	732	
1011	1225		**1511**	420	BQL
1012	2740		**1512**	892	
1013	488	BQL	**1513**	926	
1014	3694		**1514**	1093	
1015	1225		**1515**	691	
2001	No sample		**2501**	461	BQL
2002	339	BQL	**2502**	2070	
2003	444	BQL	**2503**	667	
2004	576	BQL	**2504**	1562	
2005	549	BQL	**2505**	637	
2006	615	BQL	**2506**	326	BQL
2007	517	BQL	**2507**	777	
2008	811		**2508**	552	BQL
2009	648		**2509**	462	BQL
2010	517	BQL	**2510**	3087	
3001	286	BQL	**3501**	900	
3002	811		**3502**	784	
3003	391	BQL	**3503**	490	BQL
3004	1505		**3504**	667	
3005	470	BQL	**3505**	1761	
3006	1642		**3506**	1175	
3007	418	BQL	**3507**	417	BQL
3008	648		**3508**	1871	
3009	843		**3509**	327	BQL
3010	517	BQL	**3510**	1087	
4001	1352		**4501**	929	
4002	312	BQL	**4502**	1161	
4003	811		**4503**	490	BQL
4004	992		**4504**	1533	
4005	1173		**4505**	667	
4006	287	BQL	**4506**	1569	
4007	386	BQL	**4507**	776	
4008	484	BQL	**4508**	190	BQL
4009	810		**4509**	552	BQL
4010	1101		**4510**	417	BQL
4011	249	BQL	**4511**	589	BQL
4012	454	BQL	**4512**	1554	
4013	792		**4513**	959	
4014	1456		**4514**	385	BQL
4015	386	BQL	**4515**	1093	

BQL Below Limit of Quantification (<625 pg/mL)

Table 13 - Results of TSH measurements

Appendix 26

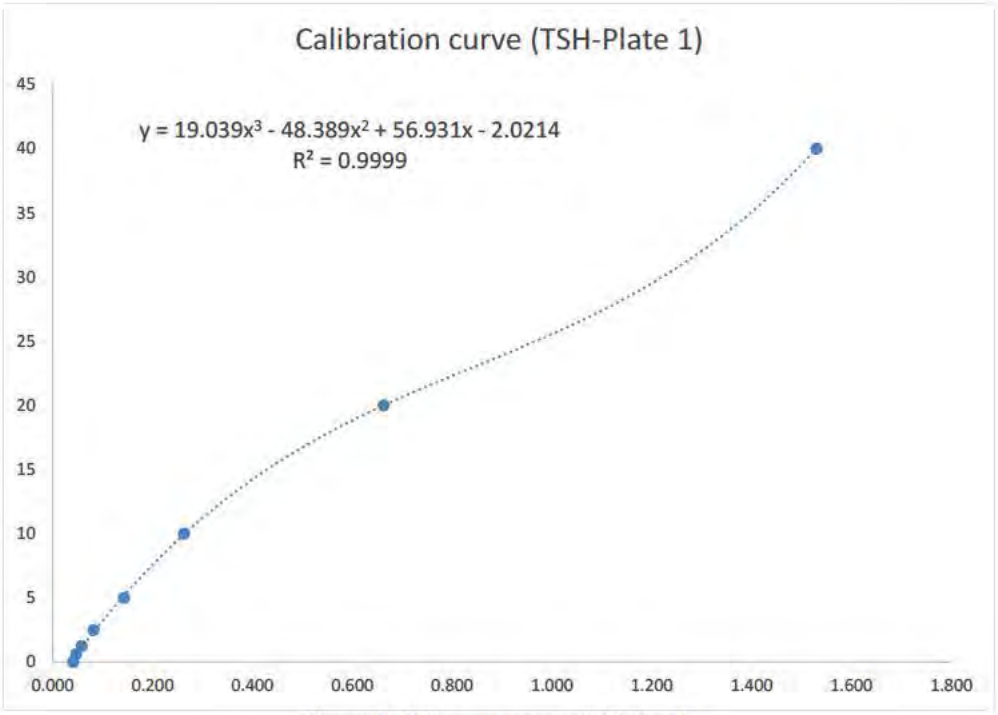


Figure 1 - Calibration curve of TSH-Plate 1

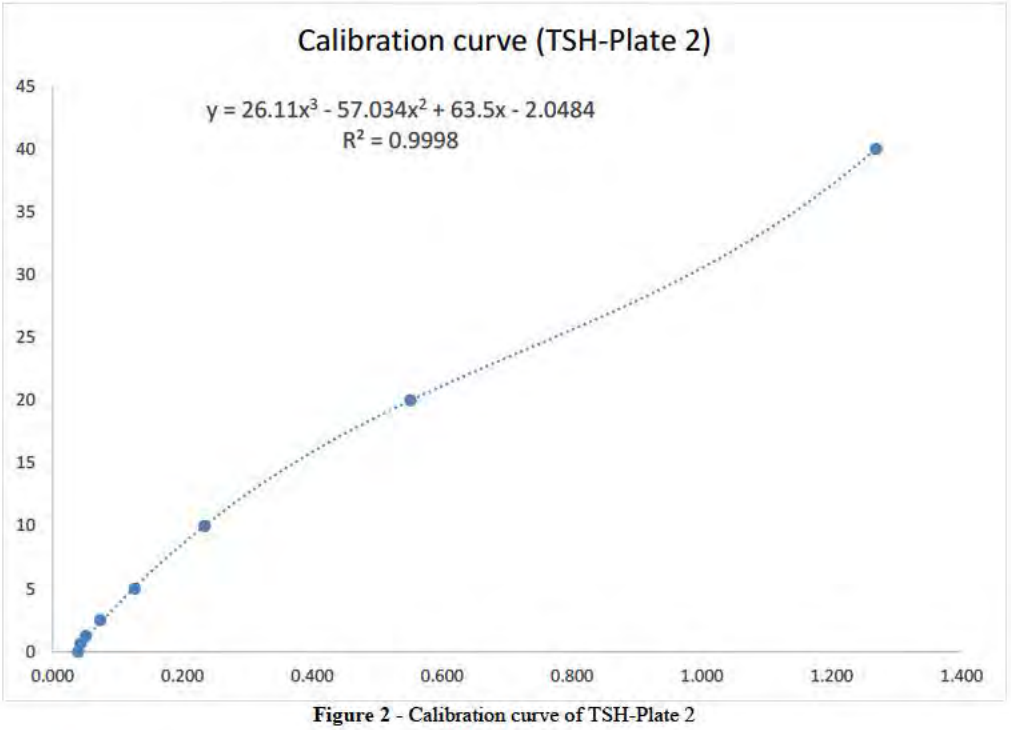


Figure 2 - Calibration curve of TSH-Plate 2

Appendix 26

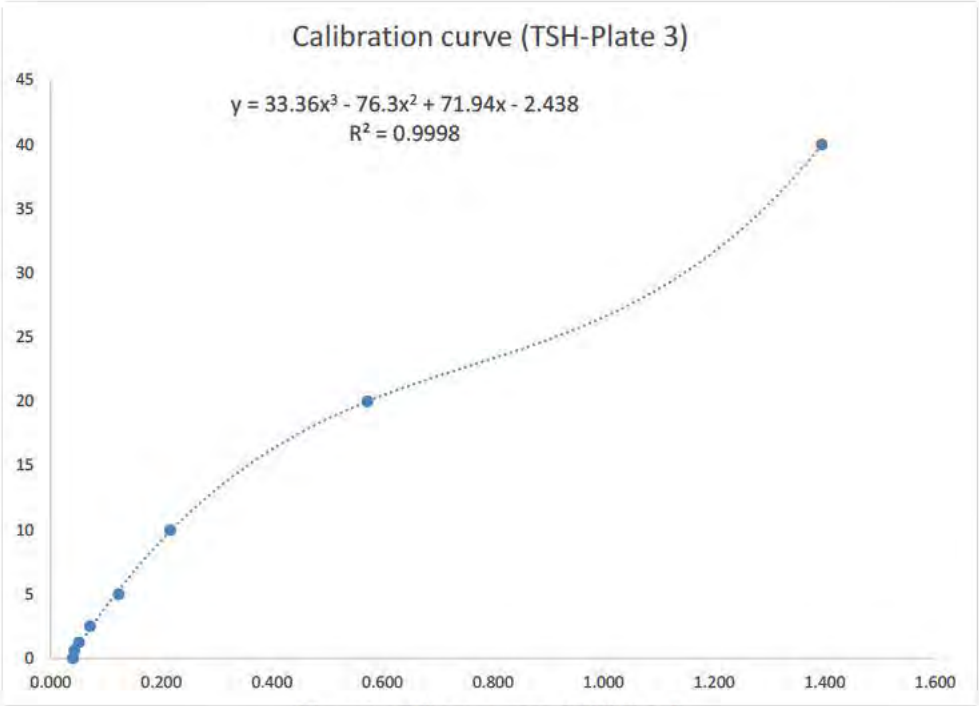


Figure 3 - Calibration curve of TSH-Plate 3

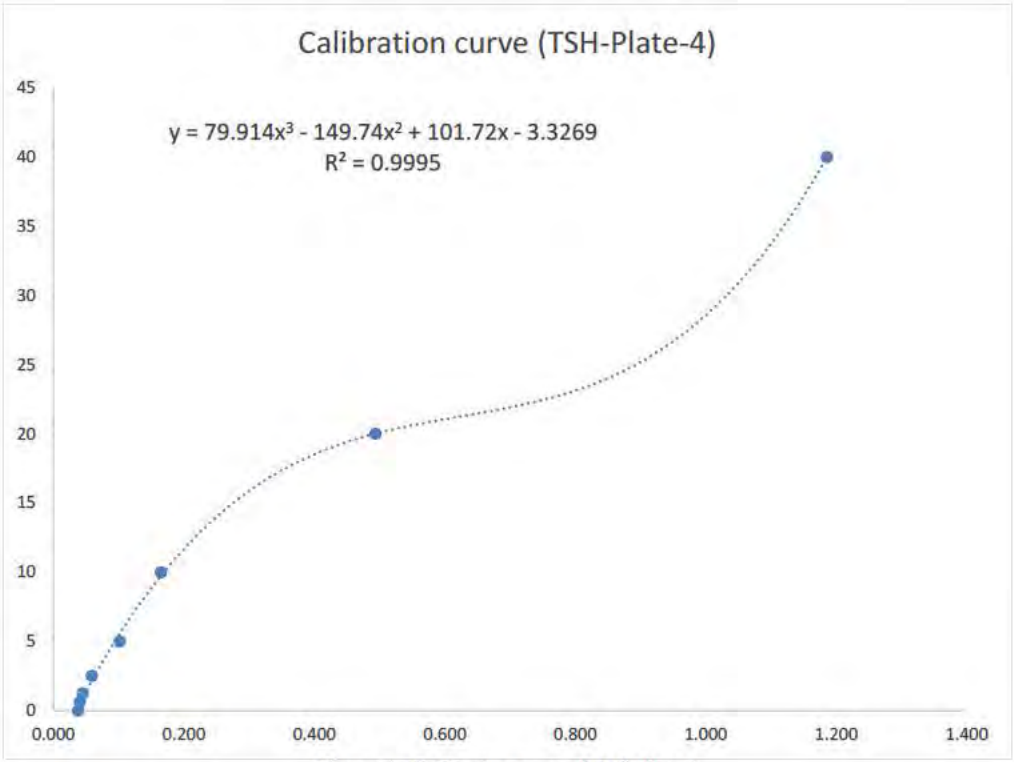


Figure 4 - Calibration curve of TSH-Plate 4

Appendix 26

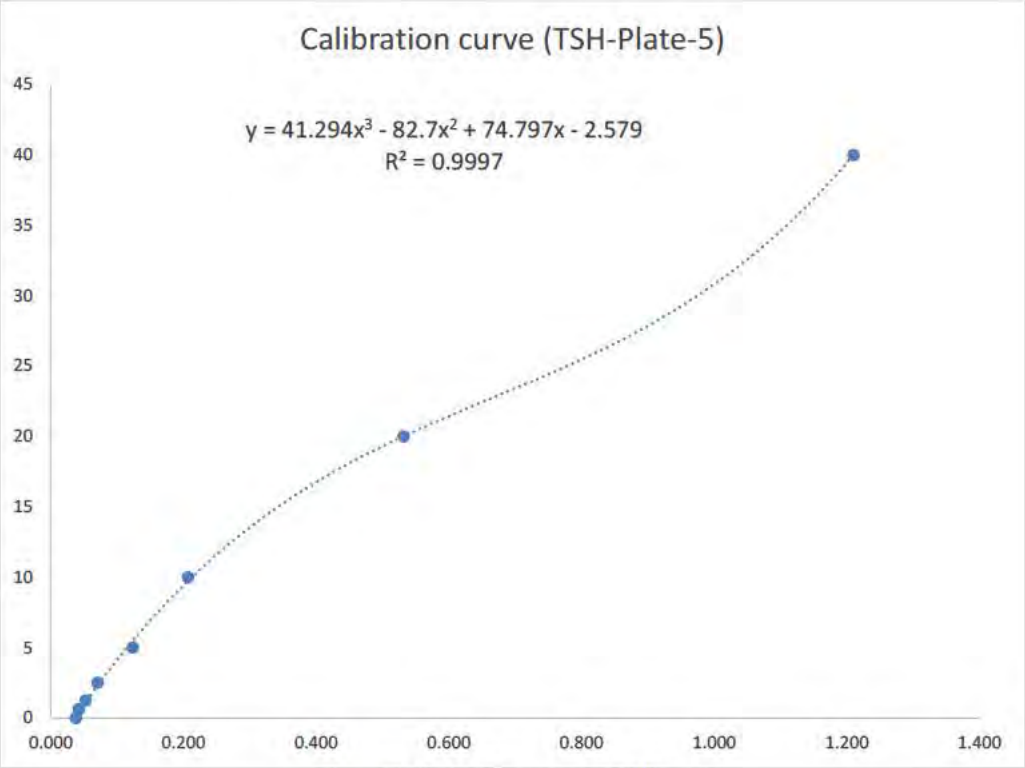


Figure 5 - Calibration curve of TSH-Plate 4

APPENDIX 1: COPY OF THE GLP CERTIFICATES OF THE TEST SITE

(b) (4), (b) (6)

(b) (4), (b) (6)

(b) (4)

APPENDIX 1: COPY OF THE GLP CERTIFICATES OF THE TEST SITE (Continued)

(b) (4), (b) (6)

Ref. no: OGYÉI/22253-9/2023
Admin.: Biró András

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

(b) (4), (b) (6)

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 27

(b) (4)

Final Report

Study Phase: Pathology

Test Facility Study No. (b) (4)

Sponsor Reference No. (b) (4)

GLP

TEST FACILITY:

(b) (4), (b)(6)

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Appendix 27

1. SUMMARY

This report presents the pathology findings for Study No. (b) (4) The objective of this study was to determine the potential toxicity of TRP Pro when given by the oral (gavage) route for 90 days to the Wistar Han IGS rat and to evaluate the potential reversibility of any findings after a 4-week recovery period.

One hundred animals were administered TRP Pro or purified water (vehicle control) via daily oral (gavage) for at least 90 days. Animals were split by sex and allocated into 4 groups (10 animals in the main study phase/5 in the recovery phase) and administered TRP Pro at 0, 500, 1000, or 2000 mg/kg/day. All animals survived to scheduled euthanasia on Day 91/92 (terminal euthanasia) and Day 120 (recovery euthanasia).

Under study conditions, daily oral (gavage) administration of TRP Pro to Wistar Han IGS rats for 90 days at doses of 500, 1000 or 2000 mg/kg/day did not result at terminal euthanasia (Day 91/92) or recovery period (Day 120) in any premature mortality, gross lesions or organ weight changes.

In addition, there was no evidence of treatment-related microscopic findings in the tissues examined at 2000 mg/kg/day. Histopathological findings were considered incidental or part of the normal background and unrelated to administration of TRP Pro.

In the absence of target tissues at microscopic evaluation of main study animals, the histological evaluation of organs/tissues in animals from the 4-week recovery euthanasia (Day 120) was not required.

2. INTRODUCTION

This report presents the pathology findings in rats assigned to Study No. (b) (4) The objective of this study was to determine the potential toxicity of TRP Pro when given by the oral (gavage) route for 90 days to the Wistar Han IGS rat and to evaluate the potential reversibility of any findings after a 4-week recovery period.

3. MATERIALS AND METHODS

Experimental procedures applicable to pathology investigations are summarized in Text Table 1.

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume[a] (mL/kg)	Dose Concentration (mg/mL)	Number of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Vehicle control	0	10	0	10	10	5	5
2	Test item	500	10	50	10	10	-	-
3	Test item	1000	10	100	10	10	-	-
4	Test item	2000	10	200	10	10	5	5

- = Not applicable.
[a] Based on the most recent body weight measurement.

A complete gross pathological examination was performed on all animals and organ weights were recorded, as specified in the Study Plan. A detailed microscopic evaluation was performed in animals from control and high dose groups in the Main Study, and all gross lesions from animals in all groups. Efforts were made to evaluate all protocol-required tissues microscopically; however, it is not always feasible for every protocol-required tissue to be present on every slide. Protocol-required tissues that were not examined were documented in the histopathology data. Since their number remained low, these missing tissues did not affect the outcome or interpretation of the pathology report.

A pathology peer review was conducted by (b)(6) Pathology Diplomate ECVP.

4. RESULTS AND DISCUSSIONS

4.1. Mortality

There were no unscheduled deaths during the course of this study.

4.2. Gross Pathology

4.2.1. Terminal Euthanasia Animals (Day 91/92)

(Table 1 and Appendix 2)

No test item-related gross findings were noted.

The gross findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in control and treated animals and, therefore, were considered unrelated to administration of TRP Pro.

4.2.2. Recovery Euthanasia Animals (Day 120)

(Table 1 and Appendix 2)

No test item-related gross findings were noted.

The gross findings observed were considered incidental, of the nature commonly observed in this strain and age of rats and/or were of similar incidence in control and treated animals and, therefore, were considered unrelated to administration of TRP Pro.

4.3. Organ Weights

4.3.1. Terminal Euthanasia Animals (Day 91/92)

(Table 2 and Appendix 1)

No test item-related organ weight changes were noted.

There were isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. In addition, no histological findings were accounted for these weight variations. Thus, the organ weight differences observed were considered incidental or related to terminal body weight differences and unrelated to administration of TRP Pro.

4.3.2. Recovery Euthanasia Animals (Day 120)

(Table 2 and Appendix 1)

No test item-related organ weight changes were noted.

Occasional organ weight values were statistically different from their respective controls. However, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, the organ weight differences observed were considered incidental and/or related to terminal body weight differences and unrelated to administration of TRP Pro.

4.4. Histopathology

4.4.1. Terminal Euthanasia Animals (Day 91/92)

(Table 3 and Appendix 2)

There was no evidence of test item-related microscopic findings in examined tissues.

The microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of Wistar Han IGS rats, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered unrelated to administration of TRP Pro.

4.4.2. Recovery Euthanasia Animals (Day 120)

(Table 3 and Appendix 2)

There was no evidence of test item-related microscopic findings in gross lesions examined at recovery euthanasia (Day 120).

5. CONCLUSIONS

Daily oral (gavage) administration of TRP Pro to Wistar Han IGS rats for 90 days at doses of 500, 1000 or 2000 mg/kg/day did not result at terminal euthanasia (Day 91/92) or recovery period (Day 120) in any premature mortality, gross lesions or organ weight changes.

In addition, there was no evidence of treatment-related microscopic findings in the tissues examined at 2000 mg/kg/day. Histopathological findings were considered incidental or part of the normal background and unrelated to administration of TRP Pro.

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
ARTERY, AORTA								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BODY CAVITY, NASAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE MARROW, STERNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE, FEMUR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE, STERNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BRAIN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
CERVIX								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
EPIDIDYMIS, LEFT								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	9	.	.	.	.
Small	0	0	0	1	.	.	.	.
EPIDIDYMIS, RIGHT								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
ESOPHAGUS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BRAIN, OLFACTORY BULB								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
EYE								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GALT								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GANGLION, DORSAL ROOT, LUMBAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, ADRENAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, CLITORAL								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
GLAND, COAGULATING								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
GLAND, HARDERIAN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, LACRIMAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, MAMMARY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PARATHYROID								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PITUITARY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, PREPUTIAL								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
GLAND, PROSTATE								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
GLAND, SALIVARY, MANDIBULAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, SALIVARY, PAROTID								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, SALIVARY, SUBLINGUAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, SEMINAL VESICLE								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
GLAND, THYROID								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, ZYMBALS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
HEART								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
JOINT, FEMOROTIBIAL, LEFT								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
KIDNEY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	9	9	10	10	8
Discoloration, pale	0	0	0	1	1	0	0	2
LARGE INTESTINE, CECUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARGE INTESTINE, COLON								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARGE INTESTINE, RECTUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARYNX								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LIVER								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	9	10	9	10	10	10	10
Hernia; medial lobe	0	1	0	1	0	0	0	0
Focus, dark; medial lobe	0	0	0	1	0	0	0	0
Focus, pale; medial lobe	1	0	0	0	0	0	0	0
LUNG								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LYMPH NODE, MANDIBULAR, LEFT								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	8	10	10	10	10
Enlargement	0	0	0	2	0	0	0	0
LYMPH NODE, MANDIBULAR, RIGHT								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	8	10	10	10	10

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, MANDIBULAR, RIGHT (Continued...)								
Enlargement	0	0	0	2	0	0	0	0
LYMPH NODE, MESENTERIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
MUSCLE, SKELETAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
NERVE, OPTIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
NERVE, SCIATIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
NERVE, TIBIAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
OVARY								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
OVIDUCT								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
PANCREAS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	10	10	10	10	10	10	10
Discoloration, pale	1	0	0	0	0	0	0	0
SKIN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	8	10	8	10	10	9	10
Scab; muzzle	0	1	0	0	0	0	0	0
Thin hair coat; abdominal	0	1	0	2	0	0	0	0

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SKIN (Continued...)								
Thin hair coat; thoracic,ventral	0	0	0	0	0	0	1	0
SMALL INTESTINE, DUODENUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SMALL INTESTINE, ILEUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SMALL INTESTINE, JEJUNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, CERVICAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, LUMBAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, THORACIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPLEEN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
STOMACH								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	6	6	2	8	9	9	8
Focus, dark; glandular	1	4	4	8	2	1	1	2
TESTIS, LEFT								
Small	.	.	.	1	.	.	.	.
Abnormal appearance; soft	.	.	.	1	.	.	.	.
TESTIS, RIGHT								
Submitted	10	10	10	10	.	.	.	.

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
TESTIS, RIGHT (Continued...)								
No Visible Lesions	10	10	10	9	.	.	.	.
Enlargement	0	0	0	1	.	.	.	.
THYMUS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
TONGUE								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
TRACHEA								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
URETER								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
URINARY BLADDER								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
UTERUS								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	9
Abnormal content	.	.	.	.	0	0	0	1
VAGINA								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): RECOVERY EUTHANASIA Summary: Incidence	Male		Female	
	0 mg/kg /day Group 1	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Number of Animals:	5	5	5	5
ARTERY, AORTA				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BODY CAVITY, NASAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE MARROW, STERNUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, FEMUR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, STERNUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BRAIN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
CERVIX				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
EPIDIDYMIS, LEFT				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
Small	0	0	.	.
EPIDIDYMIS, RIGHT				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
ESOPHAGUS				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BRAIN, OLFACTORY BULB				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): RECOVERY EUTHANASIA Summary: Incidence	Male		Female	
	0 mg/kg /day Group 1	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Number of Animals:	5	5	5	5
EYE				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GALT				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GANGLION, DORSAL ROOT, LUMBAR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, ADRENAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, CLITORAL				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
GLAND, COAGULATING				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
GLAND, HARDERIAN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, LACRIMAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, MAMMARY				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, PARATHYROID				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, PITUITARY				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): RECOVERY EUTHANASIA Summary: Incidence	Male		Female	
	0 mg/kg /day Group 1	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Number of Animals:	5	5	5	5
GLAND, PREPUTIAL				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
GLAND, PROSTATE				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
GLAND, SALIVARY, MANDIBULAR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, SALIVARY, PAROTID				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, SALIVARY, SUBLINGUAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, SEMINAL VESICLE				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
GLAND, THYROID				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, ZYMBALS				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
HEART				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
JOINT, FEMOROTIBIAL, LEFT				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): RECOVERY EUTHANASIA Summary: Incidence	Male		Female	
	0 mg/kg /day Group 1	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Number of Animals:	5	5	5	5
KIDNEY				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Discoloration, pale	0	0	0	0
LARGE INTESTINE, CECUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, COLON				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, RECTUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LARYNX				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LIVER				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Hernia; medial lobe	0	0	0	0
Focus, dark; medial lobe	0	0	0	0
Focus, pale; medial lobe	0	0	0	0
LUNG				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LYMPH NODE, MANDIBULAR, LEFT				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Enlargement	0	0	0	0
LYMPH NODE, MANDIBULAR, RIGHT				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): RECOVERY EUTHANASIA Summary: Incidence	Male		Female	
	0 mg/kg /day Group 1	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, MANDIBULAR, RIGHT (Continued...)				
Enlargement	0	0	0	0
LYMPH NODE, MESENTERIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
MUSCLE, SKELETAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, OPTIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, SCIATIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, TIBIAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
OVARY				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
OVIDUCT				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
PANCREAS				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Discoloration, pale	0	0	0	0
SKIN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Scab; muzzle	0	0	0	0
Thin hair coat; abdominal	0	0	0	0

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): RECOVERY EUTHANASIA Summary: Incidence	Male		Female	
	0 mg/kg /day Group 1	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Number of Animals:	5	5	5	5
SKIN (Continued...)				
Thin hair coat; thoracic,ventral	0	0	0	0
SMALL INTESTINE, DUODENUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, ILEUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, JEJUNUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, CERVICAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, LUMBAR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, THORACIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPLEEN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
STOMACH				
Submitted	5	5	5	5
No Visible Lesions	5	4	5	5
Focus, dark; glandular	0	1	0	0
TESTIS, RIGHT				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
Enlargement	0	0	.	.

Appendix 27
Table 1

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Summary of Macroscopic Pathology

(b) (4)

Removal Reason(s): RECOVERY EUTHANASIA Summary: Incidence	Male		Female	
	0 mg/kg /day Group 1	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Number of Animals:	5	5	5	5
THYMUS				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
TONGUE				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
TRACHEA				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
URETER				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
URINARY BLADDER				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
UTERUS				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
Abnormal content	.	.	0	0
VAGINA				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5

Appendix 27
Table 2

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Summary of Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Terminal Body Weight (g) [G]	Mean	418.3	402.3	383.5	395.5
	SD	28.7	23.3	30.8	33.7
	N	10	10	10	10
	%Diff	-	-3.8	-8.3	-5.5
Brain Weight (g) [G]	Mean	2.1530	2.0980	2.0986	2.0766
	SD	0.0909	0.0925	0.0991	0.0770
	N	10	10	10	10
	%Diff	-	-2.5546	-2.5267	-3.5485
Brain (%bw) [G]	Mean	0.51722	0.52232	0.54942	0.52780
	SD	0.04648	0.02442	0.03806	0.04073
	N	10	10	10	10
	%Diff	-	0.98555	6.22520	2.04451
Epididymis (Paired) (g) [G]	Mean	1.4320	1.3921	1.3733	1.2554**
	SD	0.1060	0.1059	0.0789	0.0959
	N	10	10	10	10
	%Diff	-	-2.7863	-4.0992	-12.3324
Epididymis (Paired) (%br) [G]	Mean	66.53151	66.31252	65.61006	60.57440*
	SD	4.41858	3.26671	5.28403	5.61909
	N	10	10	10	10
	%Diff	-	-0.32916	-1.38499	-8.95383
Epididymis (Paired) (%bw) [G]	Mean	0.34406	0.34623	0.35981	0.31931
	SD	0.03690	0.02143	0.03132	0.03389
	N	10	10	10	10
	%Diff	-	0.63061	4.57910	-7.19466
Epididymis, Lt (g) [G]	Mean	0.7003	0.6989	0.6936	0.6141*
	SD	0.0575	0.0546	0.0440	0.1086
	N	10	10	10	10
	%Diff	-	-0.1999	-0.9567	-12.3090
Epididymis, Left (%br) [G]	Mean	32.55293	33.29530	33.14712	29.71093
	SD	2.68612	1.80311	2.93751	5.69108
	N	10	10	10	10
	%Diff	-	2.28051	1.82531	-8.73041
Epididymis, Left (%bw) [G]	Mean	0.16814	0.17389	0.18190	0.15698
	SD	0.01769	0.01242	0.01872	0.03178
	N	10	10	10	10
	%Diff	-	3.42321	8.18417	-6.63774

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

Appendix 27
Table 2

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Summary of Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Epididymis, Rt (g) [G]	Mean	0.7317	0.6932	0.6797	0.6413**
	SD	0.0580	0.0576	0.0522	0.0709
	N	10	10	10	10
	%Diff	-	-5.2617	-7.1067	-12.3548
Epididymis, Right (%br) [G]	Mean	33.97858	33.01722	32.46293	30.86347
	SD	2.16466	1.93383	2.99921	2.93523
	N	10	10	10	10
	%Diff	-	-2.82933	-4.46060	-9.16787
Epididymis, Right (%bw) [G]	Mean	0.17592	0.17233	0.17792	0.16233
	SD	0.02097	0.01102	0.01579	0.01405
	N	10	10	10	10
	%Diff	-	-2.03847	1.13349	-7.72695
Epididymis, Cauda, Left (g) [G]	Mean	0.27336	0.27483	0.27355	0.25089
	SD	0.01639	0.02197	0.02891	0.04459
	N	10	10	10	10
	%Diff	-	0.53775	0.06951	-8.21993
Epididymis, Cauda, Left (%br) [G]	Mean	12.71210	13.08857	13.05392	12.13728
	SD	0.87197	0.66374	1.45949	2.32533
	N	10	10	10	10
	%Diff	-	2.96153	2.68893	-4.52183
Epididymis, Cauda, Left (%bw) [G]	Mean	0.06565	0.06835	0.07153	0.06403
	SD	0.00621	0.00444	0.00769	0.01236
	N	10	10	10	10
	%Diff	-	4.10384	8.94505	-2.48137
Seminal Vesicle/Coagulating Wt (g) [G]	Mean	1.4099	1.3725	1.2553	1.2618
	SD	0.2604	0.2442	0.1867	0.3203
	N	10	10	10	10
	%Diff	-	-2.6527	-10.9653	-10.5043
Seminal Vesicle/Coagulating (%br) [G]	Mean	65.35852	65.42524	59.92426	60.79095
	SD	10.57814	11.16963	9.07561	15.75286
	N	10	10	10	10
	%Diff	-	0.10209	-8.31454	-6.98848
Seminal Vesicle/Coagulating (%bw) [G]	Mean	0.33939	0.34260	0.32838	0.31942
	SD	0.07101	0.06483	0.05041	0.07899
	N	10	10	10	10
	%Diff	-	0.94646	-3.24400	-5.88295

[G] - Anova & Dunnett: ** = $p \leq 0.01$

Appendix 27
Table 2

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Summary of Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Gland, Adrenal Weight (g) [G]	Mean	0.06130	0.06098	0.06056	0.06302
	SD	0.00672	0.01021	0.01023	0.00967
	N	10	10	10	10
	%Diff	-	-0.52202	-1.20718	2.80587
Gland, Adrenal (%br) [G]	Mean	2.85029	2.90545	2.88487	3.03346
	SD	0.33026	0.46149	0.46337	0.44055
	N	10	10	10	10
	%Diff	-	1.93522	1.21319	6.42614
Gland, Adrenal (%bw) [G]	Mean	0.01471	0.01510	0.01592	0.01598
	SD	0.00187	0.00191	0.00323	0.00235
	N	10	10	10	10
	%Diff	-	2.63473	8.18717	8.62218
Gland, Pituitary Weight (g) [G]	Mean	0.00982	0.00929	0.00950	0.00944
	SD	0.00151	0.00144	0.00093	0.00133
	N	10	10	10	10
	%Diff	-	-5.39715	-3.25866	-3.86965
Gland, Pituitary (%br) [G]	Mean	0.45543	0.44171	0.45241	0.45517
	SD	0.06103	0.05744	0.03527	0.06540
	N	10	10	10	10
	%Diff	-	-3.01372	-0.66347	-0.05759
Gland, Pituitary (%bw) [G]	Mean	0.00236	0.00230	0.00248	0.00239
	SD	0.00039	0.00030	0.00017	0.00028
	N	10	10	10	10
	%Diff	-	-2.20867	5.23290	1.35604
Gland, Prostate Weight (g) [G]	Mean	0.9930	0.9473	0.9166	0.9066
	SD	0.1378	0.1306	0.1580	0.1985
	N	10	10	10	10
	%Diff	-	-4.6022	-7.6939	-8.7009
Gland, Prostate (%br) [G]	Mean	46.11262	45.09455	43.64410	43.52579
	SD	6.19842	5.22811	7.07092	8.68299
	N	10	10	10	10
	%Diff	-	-2.20780	-5.35325	-5.60981
Gland, Prostate (%bw) [G]	Mean	0.23884	0.23522	0.23955	0.22768
	SD	0.03983	0.02659	0.04012	0.03566
	N	10	10	10	10
	%Diff	-	-1.51238	0.29913	-4.67181

[G] - Anova & Dunnett

Appendix 27
Table 2

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Summary of Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Thyroid/Parathyroid Weight (g) [G]	Mean	0.01818	0.02048	0.01798	0.01696
	SD	0.00310	0.00336	0.00272	0.00373
	N	10	10	10	10
	%Diff	-	12.65127	-1.10011	-6.71067
Thyroid/Parathyroid (%br) [G]	Mean	0.84577	0.97583	0.85838	0.81706
	SD	0.14960	0.15025	0.13569	0.17755
	N	10	10	10	10
	%Diff	-	15.37712	1.49055	-3.39494
Thyroid/Parathyroid (%bw) [G]	Mean	0.00434	0.00508	0.00472	0.00434
	SD	0.00062	0.00071	0.00078	0.00111
	N	10	10	10	10
	%Diff	-	17.20147	8.74224	-0.01864
Heart Weight (g) [G]	Mean	1.1191	1.0831	1.0338	1.0295
	SD	0.1024	0.0818	0.0907	0.0902
	N	10	10	10	10
	%Diff	-	-3.2169	-7.6222	-8.0064
Heart (%br) [G]	Mean	52.12616	51.62257	49.28550	49.62243
	SD	5.92397	3.16992	3.97245	4.52364
	N	10	10	10	10
	%Diff	-	-0.96611	-5.44959	-4.80322
Heart (%bw) [G]	Mean	0.26760	0.26939	0.26971	0.26073
	SD	0.01663	0.01676	0.01324	0.01743
	N	10	10	10	10
	%Diff	-	0.66668	0.78786	-2.56698
Kidney Weight (g) [G]	Mean	2.3516	2.3637	2.3280	2.6528
	SD	0.2121	0.2610	0.2639	0.3844
	N	10	10	10	10
	%Diff	-	0.5145	-1.0036	12.8083
Kidney (%br) [G]	Mean	109.47667	112.41330	110.82382	127.56713**
	SD	11.92899	8.17220	10.40354	15.93007
	N	10	10	10	10
	%Diff	-	2.68242	1.23054	16.52449
Kidney (%bw) [G]	Mean	0.56254	0.58730	0.60714	0.66882**
	SD	0.03891	0.05223	0.05162	0.05378
	N	10	10	10	10
	%Diff	-	4.40120	7.92844	18.89189

[G] - Anova & Dunnett: ** = $p \leq 0.01$

Appendix 27
Table 2

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Summary of Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Liver Weight (g) [G]	Mean	10.2095	10.5631	10.4728	11.1473
	SD	0.6541	0.8484	1.4150	1.7258
	N	10	10	10	10
	%Diff	-	3.4634	2.5790	9.1856
Liver (%br) [G1]	Mean	475.29823	502.94327	498.00830	535.77029
	SD	41.28831	22.61800	53.95666	70.13049
	N	10	10	10	10
	%Diff	-	5.81636	4.77807	12.72297
Liver (%bw) [G]	Mean	2.44418	2.62578	2.72303**	2.80646**
	SD	0.11730	0.14736	0.20442	0.20750
	N	10	10	10	10
	%Diff	-	7.42978	11.40839	14.82190
Spleen Weight (g) [G]	Mean	0.6453	0.7342	0.6314	0.6663
	SD	0.0857	0.0779	0.0655	0.0983
	N	10	10	10	10
	%Diff	-	13.7765	-2.1540	3.2543
Spleen (%br) [G]	Mean	30.01699	34.96703**	30.07543	32.04354
	SD	4.12936	3.10450	2.61046	4.06271
	N	10	10	10	10
	%Diff	-	16.49079	0.19470	6.75133
Spleen (%bw) [G]	Mean	0.15442	0.18216**	0.16496	0.16804
	SD	0.01847	0.01162	0.01582	0.01525
	N	10	10	10	10
	%Diff	-	17.96323	6.82350	8.82041
Testis (Paired) (g) [G]	Mean	3.7271	3.6254	3.6027	3.2885**
	SD	0.3075	0.3518	0.2150	0.3358
	N	10	10	10	10
	%Diff	-	-2.7287	-3.3377	-11.7679
Testis (Paired) (%br) [G]	Mean	173.23551	172.57689	171.88060	158.68533
	SD	14.18627	12.03591	10.89811	17.94121
	N	10	10	10	10
	%Diff	-	-0.38019	-0.78212	-8.39907
Testis (Paired) (%bw) [G]	Mean	0.89254	0.90029	0.94188	0.83751
	SD	0.06975	0.05939	0.05241	0.11143
	N	10	10	10	10
	%Diff	-	0.86827	5.52781	-6.16537

[G] - Anova & Dunnett: ** = $p \leq 0.01$
[G1] - Kruskal-Wallis & Dunn

Appendix 27
Table 2

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Summary of Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Testis Left (g) [G]	Mean	1.8692	1.8123	1.8161	1.5499
	SD	0.1492	0.1785	0.1196	0.4752
	N	10	10	10	10
	%Diff	-	-3.0441	-2.8408	-17.0822
Testis, Left (%br) [G]	Mean	86.88183	86.25459	86.62245	75.13079
	SD	6.87516	5.99270	5.65268	23.22034
	N	10	10	10	10
	%Diff	-	-0.72194	-0.29853	-13.52531
Testis, Left (%bw) [G]	Mean	0.44759	0.45001	0.47474	0.39833
	SD	0.03331	0.03023	0.02837	0.12636
	N	10	10	10	10
	%Diff	-	0.54082	6.06648	-11.00520
Testis Right (g) [G]	Mean	1.8579	1.8131	1.7866	1.7386
	SD	0.1596	0.1746	0.1049	0.2627
	N	10	10	10	10
	%Diff	-	-2.4113	-3.8377	-6.4212
Testis, Right (%br) [G]	Mean	86.35368	86.32230	85.25814	83.55454
	SD	7.37401	6.12904	5.69892	10.46241
	N	10	10	10	10
	%Diff	-	-0.03634	-1.26867	-3.24148
Testis, Right (%bw) [G]	Mean	0.44495	0.45028	0.46713	0.43918
	SD	0.03672	0.02964	0.02684	0.04785
	N	10	10	10	10
	%Diff	-	1.19767	4.98593	-1.29679
Thymus Weight (g) [G]	Mean	0.3672	0.3985	0.3307	0.3285
	SD	0.0596	0.0837	0.0559	0.0752
	N	10	10	10	10
	%Diff	-	8.5240	-9.9401	-10.5392
Thymus (%br) [G]	Mean	17.14140	18.96729	15.77783	15.83035
	SD	3.20304	3.70971	2.66146	3.64031
	N	10	10	10	10
	%Diff	-	10.65192	-7.95485	-7.64842
Thymus (%bw) [G]	Mean	0.08763	0.09906	0.08665	0.08280
	SD	0.01175	0.02021	0.01631	0.01725
	N	10	10	10	10
	%Diff	-	13.04027	-1.12244	-5.51378

[G] - Anova & Dunnett

Appendix 27
Table 2

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Summary of Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Terminal Body Weight (g) [G]	Mean	243.8	250.2	259.1	251.4
	SD	22.7	15.0	15.3	21.3
	N	10	10	10	10
	%Diff	-	2.6	6.3	3.1
Brain Weight (g) [G]	Mean	1.9634	1.9393	1.9876	1.9284
	SD	0.0860	0.0385	0.0884	0.0581
	N	10	10	10	10
	%Diff	-	-1.2275	1.2326	-1.7826
Brain (%bw) [G]	Mean	0.80961	0.77752	0.76977	0.77181
	SD	0.05598	0.04742	0.06064	0.06633
	N	10	10	10	10
	%Diff	-	-3.96301	-4.92043	-4.66818
Gland, Adrenal Weight (g) [G]	Mean	0.06471	0.06194	0.06890	0.06549
	SD	0.01435	0.00944	0.01160	0.00757
	N	10	10	10	10
	%Diff	-	-4.28064	6.47504	1.20538
Gland, Adrenal (%br) [G]	Mean	3.30210	3.19794	3.45577	3.39676
	SD	0.74764	0.51600	0.48447	0.39065
	N	10	10	10	10
	%Diff	-	-3.15426	4.65379	2.86669
Gland, Adrenal (%bw) [G1]	Mean	0.02673	0.02474	0.02673	0.02619
	SD	0.00629	0.00337	0.00489	0.00346
	N	10	10	10	10
	%Diff	-	-7.47277	-0.02322	-2.04509
Gland, Pituitary Weight (g) [G]	Mean	0.01320	0.01134	0.01281	0.01359
	SD	0.00171	0.00254	0.00168	0.00194
	N	10	10	10	10
	%Diff	-	-14.09091	-2.95455	2.95455
Gland, Pituitary (%br) [G]	Mean	0.67241	0.58576	0.64475	0.70557
	SD	0.08178	0.13574	0.08200	0.10420
	N	10	10	10	10
	%Diff	-	-12.88650	-4.11283	4.93143
Gland, Pituitary (%bw) [G]	Mean	0.00544	0.00452*	0.00495	0.00539
	SD	0.00071	0.00088	0.00062	0.00049
	N	10	10	10	10
	%Diff	-	-16.83311	-8.97810	-0.82181

[G] - Anova & Dunnett: * = $p \leq 0.05$
[G1] - Kruskal-Wallis & Dunn

Appendix 27
Table 2

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Summary of Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Thyroid/Parathyroid Weight (g) [G]	Mean	0.01364	0.01575	0.01709	0.01660
	SD	0.00411	0.00440	0.00423	0.00372
	N	10	10	10	10
	%Diff	-	15.46921	25.29326	21.70088
Thyroid/Parathyroid (%br) [G]	Mean	0.69433	0.81341	0.86281	0.86284
	SD	0.20342	0.22908	0.22372	0.20125
	N	10	10	10	10
	%Diff	-	17.15029	24.26473	24.26921
Thyroid/Parathyroid (%bw) [G]	Mean	0.00565	0.00635	0.00664	0.00663
	SD	0.00178	0.00198	0.00183	0.00150
	N	10	10	10	10
	%Diff	-	12.25222	17.53834	17.23260
Heart Weight (g) [G]	Mean	0.7529	0.7731	0.7854	0.7967
	SD	0.0598	0.1004	0.0665	0.0592
	N	10	10	10	10
	%Diff	-	2.6830	4.3166	5.8175
Heart (%br) [G]	Mean	38.37800	39.88381	39.55709	41.33342
	SD	3.05079	5.30855	3.44090	3.16928
	N	10	10	10	10
	%Diff	-	3.92362	3.07230	7.70081
Heart (%bw) [G]	Mean	0.31078	0.30793	0.30381	0.31739
	SD	0.03435	0.02206	0.02846	0.01508
	N	10	10	10	10
	%Diff	-	-0.91655	-2.24164	2.12761
Kidney Weight (g) [G]	Mean	1.5622	1.6450	1.8118**	1.8835**
	SD	0.1339	0.1205	0.1413	0.1693
	N	10	10	10	10
	%Diff	-	5.3002	15.9775	20.5671
Kidney (%br) [G]	Mean	79.55030	84.84747	91.29433**	97.67473**
	SD	5.60960	6.36341	7.93815	8.25829
	N	10	10	10	10
	%Diff	-	6.65890	14.76302	22.78361
Kidney (%bw) [G]	Mean	0.64332	0.65769	0.70103	0.75133**
	SD	0.05463	0.03374	0.06310	0.06664
	N	10	10	10	10
	%Diff	-	2.23256	8.97017	16.78936

[G] - Anova & Dunnett: ** = $p \leq 0.01$

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Table 2

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Summary of Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Liver Weight (g) [G]	Mean	6.0859	6.5614	7.0608**	7.3082**
	SD	0.6020	0.6926	0.5315	0.5741
	N	10	10	10	10
	%Diff	-	7.8131	16.0190	20.0841
Liver (%br) [G]	Mean	309.95736	338.61121	355.71933**	379.22787**
	SD	27.10739	37.96635	28.91143	31.04805
	N	10	10	10	10
	%Diff	-	9.24445	14.76396	22.34840
Liver (%bw) [G]	Mean	2.50152	2.62174	2.72878*	2.91092**
	SD	0.17695	0.21810	0.19707	0.13930
	N	10	10	10	10
	%Diff	-	4.80600	9.08515	16.36618
Ovary Paired (g) [G]	Mean	0.1081	0.1156	0.1199	0.1289
	SD	0.0155	0.0264	0.0239	0.0235
	N	10	10	10	10
	%Diff	-	6.9380	10.9158	19.2414
Ovary Paired (%br) [G]	Mean	5.51559	5.95855	6.02000	6.69668
	SD	0.84961	1.34836	1.11021	1.29887
	N	10	10	10	10
	%Diff	-	8.03101	9.14514	21.41368
Ovary Paired (%bw) [G]	Mean	0.04473	0.04609	0.04642	0.05110
	SD	0.00826	0.00956	0.00977	0.00590
	N	10	10	10	10
	%Diff	-	3.04141	3.78971	14.24650
Spleen Weight (g) [G]	Mean	0.4851	0.4806	0.5466	0.5602
	SD	0.1048	0.0574	0.0995	0.0942
	N	10	10	10	10
	%Diff	-	-0.9276	12.6778	15.4813
Spleen (%br) [G]	Mean	24.64953	24.78179	27.43972	29.00446
	SD	4.83048	2.89768	4.25244	4.56312
	N	10	10	10	10
	%Diff	-	0.53659	11.31945	17.66742
Spleen (%bw) [G]	Mean	0.19830	0.19220	0.21167	0.22228
	SD	0.03198	0.02136	0.04123	0.02830
	N	10	10	10	10
	%Diff	-	-3.07759	6.74231	12.09258

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

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Table 2

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Summary of Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date		0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Thymus Weight (g) [G]	Mean	0.3116	0.3069	0.3233	0.3352
	SD	0.0430	0.0584	0.0655	0.0613
	N	10	10	10	10
	%Diff	-	-1.5083	3.7548	7.5738
Thymus (%br) [G]	Mean	15.82067	15.80195	16.35698	17.36964
	SD	1.59481	2.83925	3.65585	3.03199
	N	10	10	10	10
	%Diff	-	-0.11833	3.38993	9.79078
Thymus (%bw) [G]	Mean	0.12758	0.12254	0.12473	0.13337
	SD	0.01011	0.02166	0.02429	0.02228
	N	10	10	10	10
	%Diff	-	-3.95122	-2.23745	4.53664
Uterus/Cervix (g) [G]	Mean	0.5996	0.7193	0.6223	0.6056
	SD	0.2730	0.2933	0.2183	0.1838
	N	10	10	10	10
	%Diff	-	19.9633	3.7859	1.0007
Uterus/Cervix (%br) [G]	Mean	30.31904	37.16794	31.42162	31.30047
	SD	13.04618	15.37045	11.47135	8.92795
	N	10	10	10	10
	%Diff	-	22.58947	3.63661	3.23703
Uterus/Cervix (%bw) [G]	Mean	0.24349	0.28955	0.23886	0.24433
	SD	0.10183	0.12524	0.07514	0.08440
	N	10	10	10	10
	%Diff	-	18.91734	-1.90116	0.34570

[G] - Anova & Dunnett

Appendix 27
Table 2

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Summary of Organ Weights: Day 120

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Terminal Body Weight (g) [G]	Mean	428.2	401.2
	SD	24.1	27.5
	N	5	5
	%Diff	-	-6.3
Brain Weight (g) [G]	Mean	2.1972	2.0950
	SD	0.0707	0.1262
	N	5	5
	%Diff	-	-4.6514
Brain (%bw) [G]	Mean	0.51376	0.52368
	SD	0.01540	0.04179
	N	5	5
	%Diff	-	1.93072
Epididymis (Paired) (g) [G]	Mean	1.6624	1.4462*
	SD	0.1501	0.0724
	N	5	5
	%Diff	-	-13.0053
Epididymis (Paired) (%br) [G]	Mean	75.63091	69.28583
	SD	5.98914	6.15032
	N	5	5
	%Diff	-	-8.38953
Epididymis (Paired) (%bw) [G]	Mean	0.38803	0.36141
	SD	0.02363	0.02324
	N	5	5
	%Diff	-	-6.86098
Epididymis, Lt (g) [G1]	Mean	0.8236	0.7130*
	SD	0.0853	0.0273
	N	5	5
	%Diff	-	-13.4288
Epididymis, Left (%br) [G]	Mean	37.47669	34.14572
	SD	3.61993	2.62819
	N	5	5
	%Diff	-	-8.88811
Epididymis, Left (%bw) [G]	Mean	0.19231	0.17833
	SD	0.01635	0.01290
	N	5	5
	%Diff	-	-7.26930

[G] - Anova & Dunnett: * = $p \leq 0.05$
[G1] - Kruskal-Wallis & Dunn: * = $p \leq 0.05$

Appendix 27
Table 2

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Summary of Organ Weights: Day 120

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Epididymis, Rt (g) [G]	Mean	0.8388	0.7332*
	SD	0.0721	0.0510
	N	5	5
	%Diff	-	-12.5894
Epididymis, Right (%br) [G]	Mean	38.15422	35.14011
	SD	2.71091	3.71565
	N	5	5
	%Diff	-	-7.89980
Epididymis, Right (%bw) [G]	Mean	0.19572	0.18308
	SD	0.00891	0.01224
	N	5	5
	%Diff	-	-6.45978
Epididymis, Cauda, Left (g) [G]	Mean	0.35132	0.30450*
	SD	0.03256	0.02334
	N	5	5
	%Diff	-	-13.32688
Epididymis, Cauda, Left (%br) [G]	Mean	15.99033	14.56997
	SD	1.39828	1.30502
	N	5	5
	%Diff	-	-8.88263
Epididymis, Cauda, Left (%bw) [G]	Mean	0.08206	0.07611
	SD	0.00620	0.00667
	N	5	5
	%Diff	-	-7.25628
Seminal Vesicle/Coagulating Wt (g) [G]	Mean	1.6744	1.5390
	SD	0.4515	0.2069
	N	5	5
	%Diff	-	-8.0865
Seminal Vesicle/Coagulating (%br) [G]	Mean	76.07138	73.48478
	SD	20.20471	9.15321
	N	5	5
	%Diff	-	-3.40023
Seminal Vesicle/Coagulating (%bw) [G]	Mean	0.39049	0.38333
	SD	0.10483	0.04111
	N	5	5
	%Diff	-	-1.83409

[G] - Anova & Dunnett: * = $p \leq 0.05$

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Summary of Organ Weights: Day 120

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Gland, Adrenal Weight (g) [G]	Mean	0.06994	0.05744
	SD	0.01587	0.00519
	N	5	5
	%Diff	-	-17.87246
Gland, Adrenal (%br) [G]	Mean	3.16958	2.74524
	SD	0.63192	0.23479
	N	5	5
	%Diff	-	-13.38786
Gland, Adrenal (%bw) [G1]	Mean	0.01626	0.01431
	SD	0.00318	0.00064
	N	5	5
	%Diff	-	-12.00309
Gland, Pituitary Weight (g) [G]	Mean	0.01000	0.00900
	SD	0.00135	0.00135
	N	5	5
	%Diff	-	-10.00000
Gland, Pituitary (%br) [G]	Mean	0.45602	0.42827
	SD	0.06761	0.04636
	N	5	5
	%Diff	-	-6.08546
Gland, Pituitary (%bw) [G]	Mean	0.00235	0.00225
	SD	0.00041	0.00033
	N	5	5
	%Diff	-	-4.47237
Gland, Prostate Weight (g) [G]	Mean	1.0488	0.8962
	SD	0.1891	0.1738
	N	5	5
	%Diff	-	-14.5500
Gland, Prostate (%br) [G]	Mean	47.59860	42.83935
	SD	7.70765	8.12621
	N	5	5
	%Diff	-	-9.99873
Gland, Prostate (%bw) [G]	Mean	0.24393	0.22345
	SD	0.03627	0.04018
	N	5	5
	%Diff	-	-8.39413

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Appendix 27
Table 2

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Summary of Organ Weights: Day 120

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Thyroid/Parathyroid Weight (g) [G]	Mean	0.01796	0.01888
	SD	0.00368	0.00109
	N	5	5
	%Diff	-	5.12249
Thyroid/Parathyroid (%br) [G1]	Mean	0.81401	0.90409
	SD	0.14234	0.08006
	N	5	5
	%Diff	-	11.06547
Thyroid/Parathyroid (%bw) [G1]	Mean	0.00417	0.00472
	SD	0.00067	0.00045
	N	5	5
	%Diff	-	13.27819
Heart Weight (g) [G1]	Mean	1.2082	1.0566*
	SD	0.0908	0.0969
	N	5	5
	%Diff	-	-12.5476
Heart (%br) [G1]	Mean	54.93688	50.61995
	SD	2.74020	6.04657
	N	5	5
	%Diff	-	-7.85798
Heart (%bw) [G1]	Mean	0.28194	0.26322*
	SD	0.00777	0.01335
	N	5	5
	%Diff	-	-6.63888
Kidney Weight (g) [G1]	Mean	2.5102	2.4754
	SD	0.2794	0.3720
	N	5	5
	%Diff	-	-1.3863
Kidney (%br) [G1]	Mean	114.09058	118.09815
	SD	10.06143	15.73158
	N	5	5
	%Diff	-	3.51263
Kidney (%bw) [G1]	Mean	0.58607	0.61569
	SD	0.05339	0.06972
	N	5	5
	%Diff	-	5.05332

[G] - Kruskal-Wallis & Dunn
[G1] - Anova & Dunnett: * = $p \leq 0.05$

Appendix 27
Table 2

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Summary of Organ Weights: Day 120

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Liver Weight (g) [G]	Mean	10.4860	9.5046
	SD	1.1640	0.7685
	N	5	5
	%Diff	-	-9.3591
Liver (%br) [G]	Mean	476.63554	454.62337
	SD	43.94123	41.18265
	N	5	5
	%Diff	-	-4.61824
Liver (%bw) [G]	Mean	2.44692	2.36850
	SD	0.21596	0.08831
	N	5	5
	%Diff	-	-3.20489
Spleen Weight (g) [G]	Mean	0.7358	0.6952
	SD	0.1102	0.0467
	N	5	5
	%Diff	-	-5.5178
Spleen (%br) [G]	Mean	33.41999	33.28044
	SD	4.34203	3.02131
	N	5	5
	%Diff	-	-0.41756
Spleen (%bw) [G]	Mean	0.17136	0.17421
	SD	0.01956	0.01998
	N	5	5
	%Diff	-	1.66412
Testis (Paired) (g) [G]	Mean	4.0552	3.6300*
	SD	0.2114	0.3377
	N	5	5
	%Diff	-	-10.4853
Testis (Paired) (%br) [G]	Mean	184.67295	173.48418
	SD	10.54670	15.30825
	N	5	5
	%Diff	-	-6.05870
Testis (Paired) (%bw) [G]	Mean	0.94947	0.90547
	SD	0.07470	0.06817
	N	5	5
	%Diff	-	-4.63415

[G] - Anova & Dunnett: * = $p \leq 0.05$

Appendix 27
Table 2

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Summary of Organ Weights: Day 120

(b) (4)

Sex: Male Day(s) Relative to Start Date		0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Testis Left (g) [G]	Mean	2.0394	1.8246
	SD	0.1321	0.1809
	N	5	5
	%Diff	-	-10.5325
Testis, Left (%br) [G]	Mean	92.85102	87.21324
	SD	5.88924	8.37369
	N	5	5
	%Diff	-	-6.07185
Testis, Left (%bw) [G]	Mean	0.47748	0.45490
	SD	0.04094	0.03418
	N	5	5
	%Diff	-	-4.72759
Testis Right (g) [G]	Mean	2.0158	1.8054*
	SD	0.1005	0.1586
	N	5	5
	%Diff	-	-10.4375
Testis, Right (%br) [G]	Mean	91.82193	86.27093
	SD	5.59531	6.99392
	N	5	5
	%Diff	-	-6.04540
Testis, Right (%bw) [G]	Mean	0.47200	0.45057
	SD	0.03722	0.03481
	N	5	5
	%Diff	-	-4.53963
Thymus Weight (g) [G]	Mean	0.2984	0.2918
	SD	0.0622	0.0783
	N	5	5
	%Diff	-	-2.2118
Thymus (%br) [G]	Mean	13.59468	14.04086
	SD	2.86915	4.28879
	N	5	5
	%Diff	-	3.28209
Thymus (%bw) [G]	Mean	0.06980	0.07242
	SD	0.01443	0.01735
	N	5	5
	%Diff	-	3.75521

[G] - Anova & Dunnett: * = $p \leq 0.05$

Appendix 27
Table 2

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Summary of Organ Weights: Day 120

(b) (4)

Sex: Female Day(s) Relative to Start Date		0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Terminal Body Weight (g) [G]	Mean	261.8	250.2
	SD	22.1	15.0
	N	5	5
	%Diff	-	-4.4
Brain Weight (g) [G]	Mean	1.9706	1.9410
	SD	0.1088	0.0935
	N	5	5
	%Diff	-	-1.5021
Brain (%bw) [G]	Mean	0.75631	0.77643
	SD	0.06526	0.02336
	N	5	5
	%Diff	-	2.66017
Gland, Adrenal Weight (g) [G]	Mean	0.06568	0.07496
	SD	0.01100	0.01796
	N	5	5
	%Diff	-	14.12911
Gland, Adrenal (%br) [G]	Mean	3.33401	3.88787
	SD	0.52957	1.08177
	N	5	5
	%Diff	-	16.61255
Gland, Adrenal (%bw) [G]	Mean	0.02522	0.03007
	SD	0.00464	0.00788
	N	5	5
	%Diff	-	19.22534
Gland, Pituitary Weight (g) [G]	Mean	0.01388	0.01200
	SD	0.00156	0.00178
	N	5	5
	%Diff	-	-13.54467
Gland, Pituitary (%br) [G]	Mean	0.70428	0.61829
	SD	0.06879	0.08843
	N	5	5
	%Diff	-	-12.20987
Gland, Pituitary (%bw) [G]	Mean	0.00530	0.00479
	SD	0.00043	0.00064
	N	5	5
	%Diff	-	-9.61980

[G] - Anova & Dunnett

Appendix 27
Table 2

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Summary of Organ Weights: Day 120

(b) (4)

Sex: Female Day(s) Relative to Start Date		0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Thyroid/Parathyroid Weight (g) [G]	Mean	0.01816	0.01616
	SD	0.00414	0.00125
	N	5	5
	%Diff	-	-11.01322
Thyroid/Parathyroid (%br) [G]	Mean	0.92510	0.83260
	SD	0.22718	0.05009
	N	5	5
	%Diff	-	-9.99894
Thyroid/Parathyroid (%bw) [G]	Mean	0.00694	0.00646
	SD	0.00161	0.00031
	N	5	5
	%Diff	-	-6.92761
Heart Weight (g) [G]	Mean	0.8184	0.7564
	SD	0.0695	0.0226
	N	5	5
	%Diff	-	-7.5758
Heart (%br) [G]	Mean	41.63729	39.05241
	SD	4.40177	2.40218
	N	5	5
	%Diff	-	-6.20810
Heart (%bw) [G1]	Mean	0.31272	0.30309
	SD	0.00913	0.01851
	N	5	5
	%Diff	-	-3.08000
Kidney Weight (g) [G]	Mean	1.6922	1.7344
	SD	0.1773	0.0870
	N	5	5
	%Diff	-	2.4938
Kidney (%br) [G]	Mean	85.73157	89.53109
	SD	5.00716	6.34078
	N	5	5
	%Diff	-	4.43188
Kidney (%bw) [G]	Mean	0.64772	0.69564
	SD	0.06004	0.05986
	N	5	5
	%Diff	-	7.39767

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Appendix 27
Table 2

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Summary of Organ Weights: Day 120

(b) (4)

Sex: Female Day(s) Relative to Start Date		0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Liver Weight (g) [G]	Mean	6.3200	6.5740
	SD	0.2357	0.2768
	N	5	5
	%Diff	-	4.0190
Liver (%br) [G]	Mean	321.53214	339.68080
	SD	22.23830	27.97815
	N	5	5
	%Diff	-	5.64443
Liver (%bw) [G]	Mean	2.42470	2.63913
	SD	0.17794	0.25158
	N	5	5
	%Diff	-	8.84359
Ovary Paired (g) [G]	Mean	0.1148	0.1106
	SD	0.0175	0.0067
	N	5	5
	%Diff	-	-3.6585
Ovary Paired (%br) [G]	Mean	5.86423	5.71175
	SD	1.08271	0.50270
	N	5	5
	%Diff	-	-2.60031
Ovary Paired (%bw) [G]	Mean	0.04428	0.04430
	SD	0.00894	0.00334
	N	5	5
	%Diff	-	0.04072
Spleen Weight (g) [G]	Mean	0.4596	0.5476
	SD	0.0581	0.0670
	N	5	5
	%Diff	-	19.1471
Spleen (%br) [G]	Mean	23.30113	28.23626*
	SD	2.32922	3.50456
	N	5	5
	%Diff	-	21.17981
Spleen (%bw) [G]	Mean	0.17589	0.21964*
	SD	0.02022	0.03211
	N	5	5
	%Diff	-	24.87263

[G] - Anova & Dunnett: * = $p \leq 0.05$

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Table 2

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Summary of Organ Weights: Day 120

(b) (4)

Sex: Female Day(s) Relative to Start Date		0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Thymus Weight (g) [G]	Mean	0.2826	0.2692
	SD	0.0376	0.0532
	N	5	5
	%Diff	-	-4.7417
Thymus (%br) [G]	Mean	14.43393	13.81065
	SD	2.41900	2.21678
	N	5	5
	%Diff	-	-4.31815
Thymus (%bw) [G]	Mean	0.10910	0.10694
	SD	0.02058	0.01454
	N	5	5
	%Diff	-	-1.98538
Uterus/Cervix (g) [G]	Mean	0.7010	0.7718
	SD	0.2378	0.2127
	N	5	5
	%Diff	-	10.0999
Uterus/Cervix (%br) [G]	Mean	35.31354	39.58536
	SD	10.75573	9.66765
	N	5	5
	%Diff	-	12.09683
Uterus/Cervix (%bw) [G]	Mean	0.26839	0.30830
	SD	0.09120	0.08059
	N	5	5
	%Diff	-	14.87072

[G] - Anova & Dunnett

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Table 3

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Summary of Microscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
ARTERY, AORTA								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BONE MARROW, STERNUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BONE, FEMUR								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BONE, STERNUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BRAIN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BRAIN, OLFACTORY BULB								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
CERVIX								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10
EPIDIDYMIS, LEFT								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	9	.	.	.	.
Depletion; sperm	0	.	.	1	.	.	.	.
.... marked	0	.	.	1	.	.	.	.
EPIDIDYMIS, RIGHT								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
ESOPHAGUS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
EYE								
Examined	10	0	0	10	10	0	0	10

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Table 3

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Summary of Microscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
EYE (Continued...)								
No Visible Lesions	10	.	.	10	10	.	.	10
GALT								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, ADRENAL								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, COAGULATING								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
GLAND, HARDERIAN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	9	10	.	.	10
Infiltration, mononuclear cell	0	.	.	1	0	.	.	0
.... minimal	0	.	.	1	0	.	.	0
GLAND, MAMMARY								
Examined	9	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	10
Not Examined: Not Present In Section.	1	0	0	0	.	.	.	.
GLAND, PARATHYROID								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, PITUITARY								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	10
Cyst; pars distalis	1	.	.	0	0	.	.	0
.... minimal	1	.	.	0	0	.	.	0
GLAND, PROSTATE								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
GLAND, SALIVARY, MANDIBULAR								

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Table 3

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Summary of Microscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, SALIVARY, MANDIBULAR (Continued...)								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, SEMINAL VESICLE								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
GLAND, THYROID								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
HEART								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	9	9	.	.	10
Infiltration, mononuclear cell; myocardial	0	.	.	1	1	.	.	0
.... minimal	0	.	.	1	1	.	.	0
JOINT, FEMOROTIBIAL, LEFT								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
KIDNEY								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	8	.	.	9	9	.	.	9
Infiltration, mononuclear cell	0	.	.	0	0	.	.	1
.... minimal	0	.	.	0	0	.	.	1
Inflammation, mononuclear cell; interstitial	0	.	.	0	1	.	.	0
.... minimal	0	.	.	0	1	.	.	0
Basophilia; tubular	1	.	.	1	1	.	.	0
.... minimal	1	.	.	1	1	.	.	0
Dilatation; pelvis	2	.	.	0	0	.	.	0
.... mild	2	.	.	0	0	.	.	0
LARGE INTESTINE, CECUM								
Examined	10	0	0	10	10	0	0	10

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Summary of Microscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LARGE INTESTINE, CECUM (Continued...)								
No Visible Lesions	10	.	.	10	10	.	.	10
LARGE INTESTINE, COLON								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
LARGE INTESTINE, RECTUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
LIVER								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	3	.	.	4	4	.	.	7
Necrosis; hepatocellular	0	.	.	1	0	.	.	0
.... mild	0	.	.	1	0	.	.	0
Infiltration, mononuclear cell	6	.	.	6	6	.	.	3
.... minimal	6	.	.	6	6	.	.	3
Fibrosis; capsular	0	.	.	1	0	.	.	0
.... minimal	0	.	.	1	0	.	.	0
Hyperplasia; bile duct	1	.	.	0	0	.	.	0
.... minimal	1	.	.	0	0	.	.	0
LUNG								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	7	.	.	10
Inflammation, mixed cell; perivascular	1	.	.	0	1	.	.	0
.... minimal	1	.	.	0	1	.	.	0
Metaplasia; alveolar, osseous	0	.	.	0	2	.	.	0
.... minimal	0	.	.	0	2	.	.	0
LYMPH NODE, MANDIBULAR, LEFT								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	5	.	.	3	6	.	.	4
Cellularity, increased; follicle	0	.	.	2	0	.	.	2
.... minimal	0	.	.	1	0	.	.	2

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Summary of Microscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, MANDIBULAR, LEFT (Continued...)								
.... mild	0	.	.	1	0	.	.	0
Cellularity, increased; plasma cell	5	.	.	5	4	.	.	4
.... minimal	5	.	.	5	4	.	.	4
LYMPH NODE, MANDIBULAR, RIGHT								
Examined	0	0	0	2	.	.	.	.
Cellularity, increased; follicle	.	.	.	1	.	.	.	.
.... mild	.	.	.	1	.	.	.	.
Cellularity, increased; alveolar, follicle	.	.	.	1	.	.	.	.
.... minimal	.	.	.	1	.	.	.	.
LYMPH NODE, MESENTERIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
MUSCLE, SKELETAL								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
NERVE, OPTIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
NERVE, SCIATIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
OVARY								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10
PANCREAS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	8	10	.	.	9
Atrophy; acinar	0	.	.	2	0	.	.	0
.... minimal	0	.	.	2	0	.	.	0

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Table 3

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Summary of Microscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
PANCREAS (Continued...)								
Infiltration, mononuclear cell; interstitial	0	.	.	0	0	.	.	1
.... minimal	0	.	.	0	0	.	.	1
Basophilic granules; decreased	1	.	.	0	0	.	.	0
.... minimal	1	.	.	0	0	.	.	0
SKIN								
Examined	10	2	0	10	10	0	1	10
No Visible Lesions	10	2	.	10	10	.	1	10
SMALL INTESTINE, DUODENUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SMALL INTESTINE, ILEUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SMALL INTESTINE, JEJUNUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SPINAL CORD								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SPLEEN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
STOMACH								
Examined	10	4	4	10	10	1	1	10
No Visible Lesions	9	4	3	7	9	0	1	9
Hemorrhage; glandular	1	0	1	1	1	1	0	1
.... minimal	1	0	1	1	1	1	0	1
Erosion; glandular	0	0	0	1	1	0	0	0
.... minimal	0	0	0	1	1	0	0	0
Edema; submucosal, glandular	0	0	0	1	0	0	0	0

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Table 3

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Summary of Microscopic Pathology

(b) (4)

Removal Reason(s): TERMINAL EUTHANASIA Summary: Incidence	Male				Female			
	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	500 mg/kg /day Group 2	1000 mg/kg /day Group 3	2000 mg/kg /day Group 4
Number of Animals:	10	10	10	10	10	10	10	10
STOMACH (Continued...)								
.... minimal	0	0	0	1	0	0	0	0
TESTIS, RIGHT								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
THYMUS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	5	7	.	.	9
Hemorrhage	0	.	.	3	1	.	.	1
.... minimal	0	.	.	1	1	.	.	1
.... mild	0	.	.	2	0	.	.	0
Apoptosis, increased	0	.	.	2	2	.	.	0
.... minimal	0	.	.	2	2	.	.	0
TONGUE								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	10
Hemorrhage	1	.	.	0	0	.	.	0
.... minimal	1	.	.	0	0	.	.	0
TRACHEA								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
URINARY BLADDER								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
UTERUS								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10
VAGINA								
Examined	.	.	.	.	10	0	0	10
Diestrus	.	.	.	.	2	.	.	4
Estrus	.	.	.	.	2	.	.	2
Metestrus	.	.	.	.	5	.	.	2
Proestrus	.	.	.	.	1	.	.	2

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Table 3

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Summary of Microscopic Pathology

(b) (4)

Removal Reason(s): RECOVERY EUTHANASIA Summary: Incidence	Male		Female	
	0 mg/kg /day Group 1	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Number of Animals:	5	5	5	5
ARTERY, AORTA				
Examined	0	0	0	0
BONE MARROW, STERNUM				
Examined	0	0	0	0
BONE, FEMUR				
Examined	0	0	0	0
BONE, STERNUM				
Examined	0	0	0	0
BRAIN				
Examined	0	0	0	0
BRAIN, OLFACTORY BULB				
Examined	0	0	0	0
CERVIX				
Examined	.	.	0	0
EPIDIDYMIS, LEFT				
Examined	0	0	.	.
EPIDIDYMIS, RIGHT				
Examined	0	0	.	.
ESOPHAGUS				
Examined	0	0	0	0
EYE				
Examined	0	0	0	0
GALT				
Examined	0	0	0	0
GLAND, ADRENAL				
Examined	0	0	0	0
GLAND, COAGULATING				
Examined	0	0	.	.
GLAND, HARDERIAN				
Examined	0	0	0	0

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Table 3

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Summary of Microscopic Pathology

(b) (4)

Removal Reason(s): RECOVERY EUTHANASIA Summary: Incidence	Male		Female	
	0 mg/kg /day Group 1	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Number of Animals:	5	5	5	5
GLAND, MAMMARY				
Examined	0	0	0	0
Not Examined: Not Present In Section.	0	0	.	.
GLAND, PARATHYROID				
Examined	0	0	0	0
GLAND, PITUITARY				
Examined	0	0	0	0
GLAND, PROSTATE				
Examined	0	0	.	.
GLAND, SALIVARY, MANDIBULAR				
Examined	0	0	0	0
GLAND, SEMINAL VESICLE				
Examined	0	0	.	.
GLAND, THYROID				
Examined	0	0	0	0
HEART				
Examined	0	0	0	0
JOINT, FEMOROTIBIAL, LEFT				
Examined	0	0	0	0
KIDNEY				
Examined	0	0	0	0
LARGE INTESTINE, CECUM				
Examined	0	0	0	0
LARGE INTESTINE, COLON				
Examined	0	0	0	0
LARGE INTESTINE, RECTUM				
Examined	0	0	0	0
LIVER				
Examined	0	0	0	0

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Table 3

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Summary of Microscopic Pathology

(b) (4)

Removal Reason(s): RECOVERY EUTHANASIA Summary: Incidence	Male		Female	
	0 mg/kg /day Group 1	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Number of Animals:	5	5	5	5
LUNG				
Examined	0	0	0	0
LYMPH NODE, MANDIBULAR, LEFT				
Examined	0	0	0	0
LYMPH NODE, MANDIBULAR, RIGHT				
Examined	0	0	.	.
LYMPH NODE, MESENTERIC				
Examined	0	0	0	0
MUSCLE, SKELETAL				
Examined	0	0	0	0
NERVE, OPTIC				
Examined	0	0	0	0
NERVE, SCIATIC				
Examined	0	0	0	0
OVARY				
Examined	.	.	0	0
PANCREAS				
Examined	0	0	0	0
SKIN				
Examined	0	0	0	0
SMALL INTESTINE, DUODENUM				
Examined	0	0	0	0
SMALL INTESTINE, ILEUM				
Examined	0	0	0	0
SMALL INTESTINE, JEJUNUM				
Examined	0	0	0	0
SPINAL CORD				
Examined	0	0	0	0

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Table 3

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Summary of Microscopic Pathology

(b) (4)

Removal Reason(s): RECOVERY EUTHANASIA Summary: Incidence	Male		Female	
	0 mg/kg /day Group 1	2000 mg/kg /day Group 4	0 mg/kg /day Group 1	2000 mg/kg /day Group 4
Number of Animals:	5	5	5	5
SPLEEN				
Examined	0	0	0	0
STOMACH				
Examined	0	1	0	0
No Visible Lesions	.	1	.	.
Hemorrhage; glandular	.	0	.	.
.... minimal	.	0	.	.
Erosion; glandular	.	0	.	.
.... minimal	.	0	.	.
Edema; submucosal, glandular	.	0	.	.
.... minimal	.	0	.	.
TESTIS, RIGHT				
Examined	0	0	.	.
THYMUS				
Examined	0	0	0	0
TONGUE				
Examined	0	0	0	0
TRACHEA				
Examined	0	0	0	0
URINARY BLADDER				
Examined	0	0	0	0
UTERUS				
Examined	.	.	0	0
VAGINA				
Examined	.	.	0	0

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Epididymis (Paired) (g)	Epididymis (Paired) (%br)	Epididymis (Paired) (%bw)
	-	-	-	-	-	-
1001	437	2.102	0.4810	1.525	72.5500	0.3490
1002	437	2.233	0.5110	1.351	60.5016	0.3092
1003	363	2.226	0.6132	1.410	63.3423	0.3884
1004	455	2.142	0.4708	1.314	61.3445	0.2888
1005	395	2.149	0.5441	1.473	68.5435	0.3729
1006	415	2.306	0.5557	1.525	66.1318	0.3675
1007	394	2.030	0.5152	1.354	66.6995	0.3437
1008	407	2.182	0.5361	1.581	72.4565	0.3885
1009	446	2.150	0.4821	1.516	70.5116	0.3399
1010	434	2.010	0.4631	1.271	63.2338	0.2929
Mean	418.3	2.1530	0.51722	1.4320	66.53151	0.34406
SD	28.7	0.0909	0.04648	0.1060	4.41858	0.03690
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Epididymis Left (g)	Epididymis Left (%br)	Epididymis Left (%bw)	Epididymis Right (g)	Epididymis Right (%br)	Epididymis Right (%bw)
	-	-	-	-	-	-
1001	0.771	36.6794	0.1764	0.754	35.8706	0.1725
1002	0.677	30.3180	0.1549	0.674	30.1836	0.1542
1003	0.643	28.8859	0.1771	0.767	34.4564	0.2113
1004	0.630	29.4118	0.1385	0.684	31.9328	0.1503
1005	0.750	34.9000	0.1899	0.723	33.6436	0.1830
1006	0.730	31.6565	0.1759	0.795	34.4753	0.1916
1007	0.679	33.4483	0.1723	0.675	33.2512	0.1713
1008	0.767	35.1512	0.1885	0.814	37.3052	0.2000
1009	0.736	34.2326	0.1650	0.780	36.2791	0.1749
1010	0.620	30.8458	0.1429	0.651	32.3881	0.1500
Mean	0.7003	32.55293	0.16814	0.7317	33.97858	0.17592
SD	0.0575	2.68612	0.01769	0.0580	2.16466	0.02097
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Epididymis Cauda, Left (g)	Epididymis Cauda, Left (%br)	Epididymis Cauda, Left (%bw)	Seminal Ves/ Coagulating (g)	Seminal Ves/ Coagul (%br)	Seminal Ves/ Coagul (%bw)
	-	-	-	-	-	-
1001	0.2867	13.6394	0.0656	1.486	70.6946	0.3400
1002	0.2805	12.5616	0.0642	1.087	48.6789	0.2487
1003	0.2539	11.4061	0.0699	1.399	62.8482	0.3854
1004	0.2630	12.2782	0.0578	1.191	55.6022	0.2618
1005	0.2794	13.0014	0.0707	1.520	70.7306	0.3848
1006	0.2836	12.2984	0.0683	1.958	84.9089	0.4718
1007	0.2941	14.4877	0.0746	1.149	56.6010	0.2916
1008	0.2846	13.0431	0.0699	1.650	75.6187	0.4054
1009	0.2650	12.3256	0.0594	1.354	62.9767	0.3036
1010	0.2428	12.0796	0.0559	1.305	64.9254	0.3007
Mean	0.27336	12.71210	0.06565	1.4099	65.35852	0.33939
SD	0.01639	0.87197	0.00621	0.2604	10.57814	0.07101
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)
	-	-	-	-	-	-
1001	0.0646	3.0733	0.0148	0.0108	0.5138	0.0025
1002	0.0601	2.6914	0.0138	0.0090	0.4030	0.0021
1003	0.0594	2.6685	0.0164	0.0093	0.4178	0.0026
1004	0.0604	2.8198	0.0133	0.0094	0.4388	0.0021
1005	0.0703	3.2713	0.0178	0.0098	0.4560	0.0025
1006	0.0664	2.8794	0.0160	0.0131	0.5681	0.0032
1007	0.0491	2.4187	0.0125	0.0074	0.3645	0.0019
1008	0.0606	2.7773	0.0149	0.0107	0.4904	0.0026
1009	0.0529	2.4605	0.0119	0.0088	0.4093	0.0020
1010	0.0692	3.4428	0.0159	0.0099	0.4925	0.0023
Mean	0.06130	2.85029	0.01471	0.00982	0.45543	0.00236
SD	0.00672	0.33026	0.00187	0.00151	0.06103	0.00039
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Gland Prostate (g)	Gland Prostate (%br)	Gland Prostate (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
1001	0.957	45.5281	0.2190	0.0201	0.9562	0.0046
1002	0.998	44.6932	0.2284	0.0219	0.9807	0.0050
1003	0.913	41.0153	0.2515	0.0144	0.6469	0.0040
1004	0.937	43.7442	0.2059	0.0210	0.9804	0.0046
1005	1.243	57.8409	0.3147	0.0210	0.9772	0.0053
1006	0.993	43.0616	0.2393	0.0176	0.7632	0.0042
1007	1.018	50.1478	0.2584	0.0134	0.6601	0.0034
1008	1.075	49.2667	0.2641	0.0157	0.7195	0.0039
1009	1.088	50.6047	0.2439	0.0162	0.7535	0.0036
1010	0.708	35.2239	0.1631	0.0205	1.0199	0.0047
Mean	0.9930	46.11262	0.23884	0.01818	0.84577	0.00434
SD	0.1378	6.19842	0.03983	0.00310	0.14960	0.00062
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
1001	1.255	59.7050	0.2872	2.299	109.3720	0.5261
1002	1.115	49.9328	0.2551	2.411	107.9713	0.5517
1003	1.041	46.7655	0.2868	2.192	98.4726	0.6039
1004	1.303	60.8310	0.2864	2.528	118.0205	0.5556
1005	1.091	50.7678	0.2762	2.388	111.1215	0.6046
1006	1.041	45.1431	0.2508	2.325	100.8239	0.5602
1007	1.027	50.5911	0.2607	2.087	102.8079	0.5297
1008	0.999	45.7837	0.2455	2.022	92.6673	0.4968
1009	1.121	52.1395	0.2513	2.587	120.3256	0.5800
1010	1.198	59.6020	0.2760	2.677	133.1841	0.6168
Mean	1.1191	52.12616	0.26760	2.3516	109.47667	0.56254
SD	0.1024	5.92397	0.01663	0.2121	11.92899	0.03891
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Spleen (g)	Spleen (%br)	Spleen (%bw)
	-	-	-	-	-	-
1001	10.100	480.4948	2.3112	0.736	35.0143	0.1684
1002	10.450	467.9803	2.3913	0.822	36.8115	0.1881
1003	9.467	425.2920	2.6080	0.627	28.1671	0.1727
1004	11.552	539.3091	2.5389	0.651	30.3922	0.1431
1005	10.177	473.5691	2.5765	0.611	28.4318	0.1547
1006	9.947	431.3530	2.3969	0.613	26.5828	0.1477
1007	9.690	477.3399	2.4594	0.568	27.9803	0.1442
1008	9.556	437.9468	2.3479	0.549	25.1604	0.1349
1009	10.137	471.4884	2.2729	0.572	26.6047	0.1283
1010	11.019	548.2090	2.5389	0.704	35.0249	0.1622
Mean	10.2095	475.29823	2.44418	0.6453	30.01699	0.15442
SD	0.6541	41.28831	0.11730	0.0857	4.12936	0.01847
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Testis (Paired) (g)	Testis (Paired) (%br)	Testis (Paired) (%bw)	Testis Left (g)	Testis Left (%br)	Testis Left (%bw)
	-	-	-	-	-	-
1001	3.896	185.3473	0.8915	1.934	92.0076	0.4426
1002	3.924	175.7277	0.8979	1.976	88.4908	0.4522
1003	3.316	148.9668	0.9135	1.653	74.2588	0.4554
1004	3.960	184.8739	0.8703	1.970	91.9701	0.4330
1005	3.858	179.5254	0.9767	1.920	89.3439	0.4861
1006	3.799	164.7441	0.9154	1.907	82.6973	0.4595
1007	3.146	154.9754	0.7985	1.593	78.4729	0.4043
1008	4.124	189.0009	1.0133	2.074	95.0504	0.5096
1009	3.520	163.7209	0.7892	1.794	83.4419	0.4022
1010	3.728	185.4726	0.8590	1.871	93.0846	0.4311
Mean	3.7271	173.23551	0.89254	1.8692	86.88183	0.44759
SD	0.3075	14.18627	0.06975	0.1492	6.87516	0.03331
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Testis Right (g)	Testis Right (%br)	Testis Right (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
1001	1.962	93.3397	0.4490	0.390	18.5538	0.0892
1002	1.948	87.2369	0.4458	0.442	19.7940	0.1011
1003	1.663	74.7080	0.4581	0.317	14.2408	0.0873
1004	1.990	92.9038	0.4374	0.377	17.6004	0.0829
1005	1.938	90.1815	0.4906	0.291	13.5412	0.0737
1006	1.892	82.0468	0.4559	0.281	12.1856	0.0677
1007	1.553	76.5025	0.3942	0.398	19.6059	0.1010
1008	2.050	93.9505	0.5037	0.324	14.8488	0.0796
1009	1.726	80.2791	0.3870	0.415	19.3023	0.0930
1010	1.857	92.3881	0.4279	0.437	21.7413	0.1007
Mean	1.8579	86.35368	0.44495	0.3672	17.14140	0.08763
SD	0.1596	7.37401	0.03672	0.0596	3.20304	0.01175
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Epididymis (Paired) (g)	Epididymis (Paired) (%br)	Epididymis (Paired) (%bw)
	-	-	-	-	-	-
2001	383	2.091	0.5460	1.248	59.6844	0.3258
2002	386	2.182	0.5653	1.499	68.6984	0.3883
2003	433	2.187	0.5051	1.547	70.7362	0.3573
2004	408	2.026	0.4966	1.349	66.5844	0.3306
2005	430	2.219	0.5160	1.496	67.4178	0.3479
2006	436	2.134	0.4894	1.392	65.2296	0.3193
2007	373	1.955	0.5241	1.308	66.9054	0.3507
2008	400	2.078	0.5195	1.452	69.8749	0.3630
2009	390	2.144	0.5497	1.384	64.5522	0.3549
2010	384	1.964	0.5115	1.246	63.4420	0.3245
Mean	402.3	2.0980	0.52232	1.3921	66.31252	0.34623
SD	23.3	0.0925	0.02442	0.1059	3.26671	0.02143
N	10	10	10	10	10	10
%Diff	-3.8	-2.5546	0.98555	-2.7863	-0.32916	0.63061

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Epididymis Left (g)	Epididymis Left (%br)	Epididymis Left (%bw)	Epididymis Right (g)	Epididymis Right (%br)	Epididymis Right (%bw)
	-	-	-	-	-	-
2001	0.637	30.4639	0.1663	0.611	29.2205	0.1595
2002	0.776	35.5637	0.2010	0.723	33.1347	0.1873
2003	0.772	35.2995	0.1783	0.775	35.4367	0.1790
2004	0.665	32.8233	0.1630	0.684	33.7611	0.1676
2005	0.738	33.2582	0.1716	0.758	34.1595	0.1763
2006	0.688	32.2399	0.1578	0.704	32.9897	0.1615
2007	0.634	32.4297	0.1700	0.674	34.4757	0.1807
2008	0.747	35.9480	0.1868	0.705	33.9269	0.1763
2009	0.677	31.5765	0.1736	0.707	32.9757	0.1813
2010	0.655	33.3503	0.1706	0.591	30.0916	0.1539
Mean	0.6989	33.29530	0.17389	0.6932	33.01722	0.17233
SD	0.0546	1.80311	0.01242	0.0576	1.93383	0.01102
N	10	10	10	10	10	10
%Diff	-0.1999	2.28051	3.42321	-5.2617	-2.82933	-2.03847

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Epididymis Cauda, Left (g)	Epididymis Cauda, Left (%br)	Epididymis Cauda, Left (%bw)	Seminal Ves/ Coagulating (g)	Seminal Ves/ Coagul (%br)	Seminal Ves/ Coagul (%bw)
	-	-	-	-	-	-
2001	0.2552	12.2047	0.0666	1.591	76.0880	0.4154
2002	0.2836	12.9973	0.0735	1.396	63.9780	0.3617
2003	0.2844	13.0041	0.0657	0.930	42.5240	0.2148
2004	0.2674	13.1984	0.0655	1.121	55.3307	0.2748
2005	0.3150	14.1956	0.0733	1.684	75.8900	0.3916
2006	0.2705	12.6757	0.0620	1.525	71.4620	0.3498
2007	0.2407	12.3120	0.0645	1.493	76.3683	0.4003
2008	0.2934	14.1193	0.0734	1.332	64.1001	0.3330
2009	0.2853	13.3069	0.0732	1.537	71.6884	0.3941
2010	0.2528	12.8717	0.0658	1.116	56.8228	0.2906
Mean	0.27483	13.08857	0.06835	1.3725	65.42524	0.34260
SD	0.02197	0.66374	0.00444	0.2442	11.16963	0.06483
N	10	10	10	10	10	10
%Diff	0.53775	2.96153	4.10384	-2.6527	0.10209	0.94646

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)
	-	-	-	-	-	-
2001	0.0475	2.2716	0.0124	0.0074	0.3539	0.0019
2002	0.0592	2.7131	0.0153	0.0088	0.4033	0.0023
2003	0.0748	3.4202	0.0173	0.0101	0.4618	0.0023
2004	0.0625	3.0849	0.0153	0.0094	0.4640	0.0023
2005	0.0589	2.6543	0.0137	0.0116	0.5228	0.0027
2006	0.0786	3.6832	0.0180	0.0093	0.4358	0.0021
2007	0.0470	2.4041	0.0126	0.0070	0.3581	0.0019
2008	0.0621	2.9885	0.0155	0.0101	0.4860	0.0025
2009	0.0549	2.5606	0.0141	0.0108	0.5037	0.0028
2010	0.0643	3.2739	0.0167	0.0084	0.4277	0.0022
Mean	0.06098	2.90545	0.01510	0.00929	0.44171	0.00230
SD	0.01021	0.46149	0.00191	0.00144	0.05744	0.00030
N	10	10	10	10	10	10
%Diff	-0.52202	1.93522	2.63473	-5.39715	-3.01372	-2.20867

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Gland Prostate (g)	Gland Prostate (%br)	Gland Prostate (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
2001	1.002	47.9197	0.2616	0.0199	0.9517	0.0052
2002	1.002	45.9212	0.2596	0.0163	0.7470	0.0042
2003	0.905	41.3809	0.2090	0.0256	1.1706	0.0059
2004	0.966	47.6802	0.2368	0.0156	0.7700	0.0038
2005	1.216	54.7995	0.2828	0.0232	1.0455	0.0054
2006	1.069	50.0937	0.2452	0.0245	1.1481	0.0056
2007	0.832	42.5575	0.2231	0.0219	1.1202	0.0059
2008	0.832	40.0385	0.2080	0.0178	0.8566	0.0045
2009	0.797	37.1735	0.2044	0.0206	0.9608	0.0053
2010	0.852	43.3809	0.2219	0.0194	0.9878	0.0051
Mean	0.9473	45.09455	0.23522	0.02048	0.97583	0.00508
SD	0.1306	5.22811	0.02659	0.00336	0.15025	0.00071
N	10	10	10	10	10	10
%Diff	-4.6022	-2.20780	-1.51238	12.65127	15.37712	17.20147

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
2001	1.070	51.1717	0.2794	2.445	116.9297	0.6384
2002	1.133	51.9248	0.2935	2.550	116.8653	0.6606
2003	1.119	51.1660	0.2584	2.464	112.6658	0.5691
2004	1.155	57.0089	0.2831	2.084	102.8628	0.5108
2005	1.194	53.8080	0.2777	2.829	127.4899	0.6579
2006	1.069	50.0937	0.2452	2.596	121.6495	0.5954
2007	0.934	47.7749	0.2504	2.056	105.1662	0.5512
2008	1.147	55.1973	0.2868	2.218	106.7372	0.5545
2009	0.997	46.5019	0.2556	2.342	109.2351	0.6005
2010	1.013	51.5784	0.2638	2.053	104.5316	0.5346
Mean	1.0831	51.62257	0.26939	2.3637	112.41330	0.58730
SD	0.0818	3.16992	0.01676	0.2610	8.17220	0.05223
N	10	10	10	10	10	10
%Diff	-3.2169	-0.96611	0.66668	0.5145	2.68242	4.40120

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Spleen (g)	Spleen (%br)	Spleen (%bw)
	-	-	-	-	-	-
2001	10.256	490.4830	2.6778	0.698	33.3812	0.1822
2002	10.999	504.0788	2.8495	0.679	31.1182	0.1759
2003	10.955	500.9145	2.5300	0.792	36.2140	0.1829
2004	9.868	487.0681	2.4186	0.812	40.0790	0.1990
2005	12.326	555.4754	2.8665	0.795	35.8269	0.1849
2006	11.141	522.0712	2.5553	0.842	39.4564	0.1931
2007	9.257	473.5038	2.4818	0.608	31.0997	0.1630
2008	10.365	498.7969	2.5913	0.716	34.4562	0.1790
2009	10.507	490.0653	2.6941	0.759	35.4011	0.1946
2010	9.957	506.9756	2.5930	0.641	32.6375	0.1669
Mean	10.5631	502.94327	2.62578	0.7342	34.96703	0.18216
SD	0.8484	22.61800	0.14736	0.0779	3.10450	0.01162
N	10	10	10	10	10	10
%Diff	3.4634	5.81636	7.42978	13.7765	16.49079	17.96323

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Testis (Paired) (g)	Testis (Paired) (%br)	Testis (Paired) (%bw)	Testis Left (g)	Testis Left (%br)	Testis Left (%bw)
	-	-	-	-	-	-
2001	3.311	158.3453	0.8645	1.663	79.5313	0.4342
2002	3.569	163.5655	0.9246	1.799	82.4473	0.4661
2003	4.062	185.7339	0.9381	2.015	92.1353	0.4654
2004	3.672	181.2438	0.9000	1.821	89.8815	0.4463
2005	3.846	173.3213	0.8944	1.950	87.8774	0.4535
2006	3.878	181.7245	0.8894	1.940	90.9091	0.4450
2007	3.034	155.1918	0.8134	1.504	76.9309	0.4032
2008	3.812	183.4456	0.9530	1.920	92.3965	0.4800
2009	3.926	183.1157	1.0067	1.949	90.9049	0.4997
2010	3.144	160.0815	0.8188	1.562	79.5316	0.4068
Mean	3.6254	172.57689	0.90029	1.8123	86.25459	0.45001
SD	0.3518	12.03591	0.05939	0.1785	5.99270	0.03023
N	10	10	10	10	10	10
%Diff	-2.7287	-0.38019	0.86827	-3.0441	-0.72194	0.54082

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Testis Right (g)	Testis Right (%br)	Testis Right (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
2001	1.648	78.8140	0.4303	0.246	11.7647	0.0642
2002	1.770	81.1182	0.4585	0.498	22.8231	0.1290
2003	2.047	93.5985	0.4727	0.530	24.2341	0.1224
2004	1.851	91.3623	0.4537	0.358	17.6703	0.0877
2005	1.896	85.4439	0.4409	0.382	17.2150	0.0888
2006	1.938	90.8154	0.4445	0.355	16.6354	0.0814
2007	1.530	78.2609	0.4102	0.333	17.0332	0.0893
2008	1.892	91.0491	0.4730	0.463	22.2810	0.1158
2009	1.977	92.2108	0.5069	0.406	18.9366	0.1041
2010	1.582	80.5499	0.4120	0.414	21.0794	0.1078
Mean	1.8131	86.32230	0.45028	0.3985	18.96729	0.09906
SD	0.1746	6.12904	0.02964	0.0837	3.70971	0.02021
N	10	10	10	10	10	10
%Diff	-2.4113	-0.03634	1.19767	8.5240	10.65192	13.04027

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Epididymis (Paired) (g)	Epididymis (Paired) (%br)	Epididymis (Paired) (%bw)
	-	-	-	-	-	-
3001	409	2.120	0.5183	1.446	68.2075	0.3535
3002	403	2.073	0.5144	1.496	72.1659	0.3712
3003	373	2.037	0.5461	1.371	67.3049	0.3676
3004	402	2.134	0.5308	1.325	62.0900	0.3296
3005	350	1.920	0.5486	1.298	67.6042	0.3709
3006	445	2.159	0.4852	1.383	64.0574	0.3108
3007	356	2.034	0.5713	1.373	67.5025	0.3857
3008	352	2.054	0.5835	1.450	70.5940	0.4119
3009	382	2.288	0.5990	1.226	53.5839	0.3209
3010	363	2.167	0.5970	1.365	62.9903	0.3760
Mean	383.5	2.0986	0.54942	1.3733	65.61006	0.35981
SD	30.8	0.0991	0.03806	0.0789	5.28403	0.03132
N	10	10	10	10	10	10
%Diff	-8.3	-2.5267	6.22520	-4.0992	-1.38499	4.57910

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Epididymis Left (g)	Epididymis Left (%br)	Epididymis Left (%bw)	Epididymis Right (g)	Epididymis Right (%br)	Epididymis Right (%bw)
	-	-	-	-	-	-
3001	0.707	33.3491	0.1729	0.739	34.8585	0.1807
3002	0.715	34.4911	0.1774	0.781	37.6749	0.1938
3003	0.751	36.8679	0.2013	0.620	30.4369	0.1662
3004	0.674	31.5839	0.1677	0.651	30.5061	0.1619
3005	0.658	34.2708	0.1880	0.640	33.3333	0.1829
3006	0.695	32.1908	0.1562	0.688	31.8666	0.1546
3007	0.671	32.9892	0.1885	0.702	34.5133	0.1972
3008	0.755	36.7575	0.2145	0.695	33.8364	0.1974
3009	0.607	26.5297	0.1589	0.619	27.0542	0.1620
3010	0.703	32.4412	0.1937	0.662	30.5491	0.1824
Mean	0.6936	33.14712	0.18190	0.6797	32.46293	0.17792
SD	0.0440	2.93751	0.01872	0.0522	2.99921	0.01579
N	10	10	10	10	10	10
%Diff	-0.9567	1.82531	8.18417	-7.1067	-4.46060	1.13349

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Epididymis Cauda, Left (g)	Epididymis Cauda, Left (%br)	Epididymis Cauda, Left (%bw)	Seminal Ves/ Coagulating (g)	Seminal Ves/ Coagul (%br)	Seminal Ves/ Coagul (%bw)
	-	-	-	-	-	-
3001	0.2881	13.5896	0.0704	1.530	72.1698	0.3741
3002	0.2551	12.3058	0.0633	1.211	58.4178	0.3005
3003	0.3324	16.3181	0.0891	1.077	52.8719	0.2887
3004	0.2873	13.4630	0.0715	1.173	54.9672	0.2918
3005	0.2285	11.9010	0.0653	1.065	55.4688	0.3043
3006	0.2947	13.6498	0.0662	1.399	64.7985	0.3144
3007	0.2660	13.0777	0.0747	1.469	72.2222	0.4126
3008	0.2757	13.4226	0.0783	1.275	62.0740	0.3622
3009	0.2529	11.0533	0.0662	0.974	42.5699	0.2550
3010	0.2548	11.7582	0.0702	1.380	63.6825	0.3802
Mean	0.27355	13.05392	0.07153	1.2553	59.92426	0.32838
SD	0.02891	1.45949	0.00769	0.1867	9.07561	0.05041
N	10	10	10	10	10	10
%Diff	0.06951	2.68893	8.94505	-10.9653	-8.31454	-3.24400

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)
	-	-	-	-	-	-
3001	0.0556	2.6226	0.0136	0.0091	0.4292	0.0022
3002	0.0538	2.5953	0.0133	0.0095	0.4583	0.0024
3003	0.0635	3.1173	0.0170	0.0092	0.4516	0.0025
3004	0.0698	3.2709	0.0174	0.0112	0.5248	0.0028
3005	0.0514	2.6771	0.0147	0.0081	0.4219	0.0023
3006	0.0536	2.4826	0.0120	0.0108	0.5002	0.0024
3007	0.0469	2.3058	0.0132	0.0088	0.4326	0.0025
3008	0.0734	3.5735	0.0209	0.0089	0.4333	0.0025
3009	0.0599	2.6180	0.0157	0.0095	0.4152	0.0025
3010	0.0777	3.5856	0.0214	0.0099	0.4569	0.0027
Mean	0.06056	2.88487	0.01592	0.00950	0.45241	0.00248
SD	0.01023	0.46337	0.00323	0.00093	0.03527	0.00017
N	10	10	10	10	10	10
%Diff	-1.20718	1.21319	8.18717	-3.25866	-0.66347	5.23290

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Gland Prostate (g)	Gland Prostate (%br)	Gland Prostate (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
3001	1.235	58.2547	0.3020	0.0213	1.0047	0.0052
3002	0.795	38.3502	0.1973	0.0133	0.6416	0.0033
3003	0.705	34.6097	0.1890	0.0192	0.9426	0.0051
3004	0.899	42.1275	0.2236	0.0135	0.6326	0.0034
3005	0.941	49.0104	0.2689	0.0196	1.0208	0.0056
3006	0.950	44.0019	0.2135	0.0205	0.9495	0.0046
3007	0.717	35.2507	0.2014	0.0166	0.8161	0.0047
3008	0.898	43.7196	0.2551	0.0184	0.8958	0.0052
3009	0.974	42.5699	0.2550	0.0188	0.8217	0.0049
3010	1.052	48.5464	0.2898	0.0186	0.8583	0.0051
Mean	0.9166	43.64410	0.23955	0.01798	0.85838	0.00472
SD	0.1580	7.07092	0.04012	0.00272	0.13569	0.00078
N	10	10	10	10	10	10
%Diff	-7.6939	-5.35325	0.29913	-1.10011	1.49055	8.74224

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
3001	1.032	48.6792	0.2523	2.404	113.3962	0.5878
3002	1.047	50.5065	0.2598	2.145	103.4732	0.5323
3003	1.110	54.4919	0.2976	2.449	120.2258	0.6566
3004	1.056	49.4845	0.2627	2.593	121.5089	0.6450
3005	0.945	49.2188	0.2700	1.861	96.9271	0.5317
3006	1.226	56.7855	0.2755	2.738	126.8180	0.6153
3007	0.984	48.3776	0.2764	2.226	109.4395	0.6253
3008	0.896	43.6222	0.2545	2.069	100.7303	0.5878
3009	1.042	45.5420	0.2728	2.276	99.4755	0.5958
3010	1.000	46.1467	0.2755	2.519	116.2437	0.6939
Mean	1.0338	49.28550	0.26971	2.3280	110.82382	0.60714
SD	0.0907	3.97245	0.01324	0.2639	10.40354	0.05162
N	10	10	10	10	10	10
%Diff	-7.6222	-5.44959	0.78786	-1.0036	1.23054	7.92844

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Spleen (g)	Spleen (%br)	Spleen (%bw)
	-	-	-	-	-	-
3001	11.561	545.3302	2.8267	0.648	30.5660	0.1584
3002	10.670	514.7130	2.6476	0.684	32.9957	0.1697
3003	9.948	488.3652	2.6670	0.624	30.6333	0.1673
3004	10.897	510.6373	2.7107	0.641	30.0375	0.1595
3005	8.549	445.2604	2.4426	0.630	32.8125	0.1800
3006	13.117	607.5498	2.9476	0.646	29.9213	0.1452
3007	9.422	463.2252	2.6466	0.558	27.4336	0.1567
3008	8.495	413.5833	2.4134	0.516	25.1217	0.1466
3009	11.061	483.4353	2.8955	0.758	33.1294	0.1984
3010	11.008	507.9834	3.0325	0.609	28.1034	0.1678
Mean	10.4728	498.00830	2.72303	0.6314	30.07543	0.16496
SD	1.4150	53.95666	0.20442	0.0655	2.61046	0.01582
N	10	10	10	10	10	10
%Diff	2.5790	4.77807	11.40839	-2.1540	0.19470	6.82350

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Testis (Paired) (g)	Testis (Paired) (%br)	Testis (Paired) (%bw)	Testis Left (g)	Testis Left (%br)	Testis Left (%bw)
	-	-	-	-	-	-
3001	3.788	178.6792	0.9262	1.896	89.4340	0.4636
3002	3.530	170.2846	0.8759	1.783	86.0106	0.4424
3003	3.807	186.8925	1.0206	1.935	94.9926	0.5188
3004	3.872	181.4433	0.9632	2.013	94.3299	0.5007
3005	3.406	177.3958	0.9731	1.667	86.8229	0.4763
3006	3.806	176.2853	0.8553	1.889	87.4942	0.4245
3007	3.574	175.7129	1.0039	1.794	88.2006	0.5039
3008	3.203	155.9396	0.9099	1.644	80.0389	0.4670
3009	3.584	156.6434	0.9382	1.827	79.8514	0.4783
3010	3.457	159.5293	0.9523	1.713	79.0494	0.4719
Mean	3.6027	171.88060	0.94188	1.8161	86.62245	0.47474
SD	0.2150	10.89811	0.05241	0.1196	5.65268	0.02837
N	10	10	10	10	10	10
%Diff	-3.3377	-0.78212	5.52781	-2.8408	-0.29853	6.06648

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Testis Right (g)	Testis Right (%br)	Testis Right (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
3001	1.892	89.2453	0.4626	0.336	15.8491	0.0822
3002	1.747	84.2740	0.4335	0.360	17.3661	0.0893
3003	1.872	91.8999	0.5019	0.291	14.2857	0.0780
3004	1.859	87.1134	0.4624	0.315	14.7610	0.0784
3005	1.739	90.5729	0.4969	0.296	15.4167	0.0846
3006	1.917	88.7911	0.4308	0.327	15.1459	0.0735
3007	1.780	87.5123	0.5000	0.414	20.3540	0.1163
3008	1.559	75.9007	0.4429	0.353	17.1860	0.1003
3009	1.757	76.7920	0.4599	0.396	17.3077	0.1037
3010	1.744	80.4799	0.4804	0.219	10.1061	0.0603
Mean	1.7866	85.25814	0.46713	0.3307	15.77783	0.08665
SD	0.1049	5.69892	0.02684	0.0559	2.66146	0.01631
N	10	10	10	10	10	10
%Diff	-3.8377	-1.26867	4.98593	-9.9401	-7.95485	-1.12244

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Epididymis (Paired) (g)	Epididymis (Paired) (%br)	Epididymis (Paired) (%bw)
	-	-	-	-	-	-
4001	447	2.215	0.4955	1.102	49.7517	0.2465
4002	454	2.147	0.4729	1.406	65.4867	0.3097
4003	394	2.048	0.5198	1.194	58.3008	0.3030
4004	392	1.984	0.5061	1.197	60.3327	0.3054
4005	373	1.987	0.5327	1.381	69.5018	0.3702
4006	352	2.099	0.5963	1.257	59.8857	0.3571
4007	398	2.108	0.5296	1.303	61.8121	0.3274
4008	409	1.980	0.4841	1.298	65.5556	0.3174
4009	371	2.093	0.5642	1.258	60.1051	0.3391
4010	365	2.105	0.5767	1.158	55.0119	0.3173
Mean	395.5	2.0766	0.52780	1.2554	60.57440	0.31931
SD	33.7	0.0770	0.04073	0.0959	5.61909	0.03389
N	10	10	10	10	10	10
%Diff	-5.5	-3.5485	2.04451	-12.3324	-8.95383	-7.19466

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Epididymis Left (g)	Epididymis Left (%br)	Epididymis Left (%bw)	Epididymis Right (g)	Epididymis Right (%br)	Epididymis Right (%bw)
	-	-	-	-	-	-
4001	0.320	14.4470	0.0716	0.782	35.3047	0.1749
4002	0.697	32.4639	0.1535	0.709	33.0228	0.1562
4003	0.610	29.7852	0.1548	0.584	28.5156	0.1482
4004	0.619	31.1996	0.1579	0.578	29.1331	0.1474
4005	0.703	35.3800	0.1885	0.678	34.1218	0.1818
4006	0.611	29.1091	0.1736	0.646	30.7766	0.1835
4007	0.657	31.1670	0.1651	0.646	30.6452	0.1623
4008	0.661	33.3838	0.1616	0.637	32.1717	0.1557
4009	0.638	30.4826	0.1720	0.620	29.6226	0.1671
4010	0.625	29.6912	0.1712	0.533	25.3207	0.1460
Mean	0.6141	29.71093	0.15698	0.6413	30.86347	0.16233
SD	0.1086	5.69108	0.03178	0.0709	2.93523	0.01405
N	10	10	10	10	10	10
%Diff	-12.3090	-8.73041	-6.63774	-12.3548	-9.16787	-7.72695

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Epididymis Cauda, Left (g)	Epididymis Cauda, Left (%br)	Epididymis Cauda, Left (%bw)	Seminal Ves/ Coagulating (g)	Seminal Ves/ Coagul (%br)	Seminal Ves/ Coagul (%bw)
	-	-	-	-	-	-
4001	0.1324	5.9774	0.0296	1.249	56.3883	0.2794
4002	0.3000	13.9730	0.0661	1.573	73.2650	0.3465
4003	0.2724	13.3008	0.0691	1.063	51.9043	0.2698
4004	0.2751	13.8659	0.0702	1.115	56.1996	0.2844
4005	0.2583	12.9995	0.0692	0.819	41.2179	0.2196
4006	0.2476	11.7961	0.0703	1.325	63.1253	0.3764
4007	0.2475	11.7410	0.0622	0.991	47.0114	0.2490
4008	0.2682	13.5455	0.0656	1.848	93.3333	0.4518
4009	0.2539	12.1309	0.0684	1.051	50.2150	0.2833
4010	0.2535	12.0428	0.0695	1.584	75.2494	0.4340
Mean	0.25089	12.13728	0.06403	1.2618	60.79095	0.31942
SD	0.04459	2.32533	0.01236	0.3203	15.75286	0.07899
N	10	10	10	10	10	10
%Diff	-8.21993	-4.52183	-2.48137	-10.5043	-6.98848	-5.88295

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)
	-	-	-	-	-	-
4001	0.0815	3.6795	0.0182	0.0117	0.5282	0.0026
4002	0.0591	2.7527	0.0130	0.0096	0.4471	0.0021
4003	0.0495	2.4170	0.0126	0.0101	0.4932	0.0026
4004	0.0767	3.8659	0.0196	0.0105	0.5292	0.0027
4005	0.0553	2.7831	0.0148	0.0099	0.4982	0.0027
4006	0.0656	3.1253	0.0186	0.0092	0.4383	0.0026
4007	0.0633	3.0028	0.0159	0.0086	0.4080	0.0022
4008	0.0594	3.0000	0.0145	0.0098	0.4949	0.0024
4009	0.0627	2.9957	0.0169	0.0070	0.3344	0.0019
4010	0.0571	2.7126	0.0156	0.0080	0.3800	0.0022
Mean	0.06302	3.03346	0.01598	0.00944	0.45517	0.00239
SD	0.00967	0.44055	0.00235	0.00133	0.06540	0.00028
N	10	10	10	10	10	10
%Diff	2.80587	6.42614	8.62218	-3.86965	-0.05759	1.35604

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Gland Prostate (g)	Gland Prostate (%br)	Gland Prostate (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
4001	1.261	56.9300	0.2821	0.0159	0.7178	0.0036
4002	1.111	51.7466	0.2447	0.0135	0.6288	0.0030
4003	0.862	42.0898	0.2188	0.0134	0.6543	0.0034
4004	0.768	38.7097	0.1959	0.0187	0.9425	0.0048
4005	0.592	29.7937	0.1587	0.0139	0.6995	0.0037
4006	0.743	35.3978	0.2111	0.0207	0.9862	0.0059
4007	0.894	42.4099	0.2246	0.0242	1.1480	0.0061
4008	1.092	55.1515	0.2670	0.0153	0.7727	0.0037
4009	0.830	39.6560	0.2237	0.0200	0.9556	0.0054
4010	0.913	43.3729	0.2501	0.0140	0.6651	0.0038
Mean	0.9066	43.52579	0.22768	0.01696	0.81706	0.00434
SD	0.1985	8.68299	0.03566	0.00373	0.17755	0.00111
N	10	10	10	10	10	10
%Diff	-8.7009	-5.60981	-4.67181	-6.71067	-3.39494	-0.01864

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
4001	1.116	50.3837	0.2497	3.327	150.2032	0.7443
4002	1.181	55.0070	0.2601	3.271	152.3521	0.7205
4003	1.043	50.9277	0.2647	2.793	136.3770	0.7089
4004	0.998	50.3024	0.2546	2.714	136.7944	0.6923
4005	1.139	57.3226	0.3054	2.284	114.9472	0.6123
4006	0.950	45.2596	0.2699	2.545	121.2482	0.7230
4007	0.985	46.7268	0.2475	2.531	120.0664	0.6359
4008	1.029	51.9697	0.2516	2.505	126.5152	0.6125
4009	0.913	43.6216	0.2461	2.334	111.5146	0.6291
4010	0.941	44.7031	0.2578	2.224	105.6532	0.6093
Mean	1.0295	49.62243	0.26073	2.6528	127.56713	0.66882
SD	0.0902	4.52364	0.01743	0.3844	15.93007	0.05378
N	10	10	10	10	10	10
%Diff	-8.0064	-4.80322	-2.56698	12.8083	16.52449	18.89189

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Spleen (g)	Spleen (%br)	Spleen (%bw)
	-	-	-	-	-	-
4001	14.345	647.6298	3.2092	0.894	40.3612	0.2000
4002	14.165	659.7578	3.1200	0.708	32.9762	0.1559
4003	11.083	541.1621	2.8129	0.631	30.8105	0.1602
4004	10.437	526.0585	2.6625	0.668	33.6694	0.1704
4005	9.537	479.9698	2.5568	0.606	30.4982	0.1625
4006	9.959	474.4640	2.8293	0.505	24.0591	0.1435
4007	10.611	503.3681	2.6661	0.696	33.0171	0.1749
4008	11.323	571.8687	2.7685	0.663	33.4848	0.1621
4009	9.868	471.4763	2.6598	0.665	31.7726	0.1792
4010	10.145	481.9477	2.7795	0.627	29.7862	0.1718
Mean	11.1473	535.77029	2.80646	0.6663	32.04354	0.16804
SD	1.7258	70.13049	0.20750	0.0983	4.06271	0.01525
N	10	10	10	10	10	10
%Diff	9.1856	12.72297	14.82190	3.2543	6.75133	8.82041

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Testis (Paired) (g)	Testis (Paired) (%br)	Testis (Paired) (%bw)	Testis Left (g)	Testis Left (%br)	Testis Left (%bw)
	-	-	-	-	-	-
4001	2.597	117.2460	0.5810	0.226	10.2032	0.0506
4002	3.556	165.6265	0.7833	1.755	81.7420	0.3866
4003	3.481	169.9707	0.8835	1.752	85.5469	0.4447
4004	2.986	150.5040	0.7617	1.551	78.1754	0.3957
4005	3.393	170.7599	0.9097	1.710	86.0594	0.4584
4006	3.127	148.9757	0.8884	1.567	74.6546	0.4452
4007	3.661	173.6717	0.9198	1.839	87.2391	0.4621
4008	3.354	169.3939	0.8200	1.654	83.5354	0.4044
4009	3.634	173.6264	0.9795	1.814	86.6699	0.4889
4010	3.096	147.0784	0.8482	1.631	77.4822	0.4468
Mean	3.2885	158.68533	0.83751	1.5499	75.13079	0.39833
SD	0.3358	17.94121	0.11143	0.4752	23.22034	0.12636
N	10	10	10	10	10	10
%Diff	-11.7679	-8.39907	-6.16537	-17.0822	-13.52531	-11.00520

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Testis Right (g)	Testis Right (%br)	Testis Right (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
4001	2.371	107.0429	0.5304	0.408	18.4199	0.0913
4002	1.801	83.8845	0.3967	0.360	16.7676	0.0793
4003	1.729	84.4238	0.4388	0.306	14.9414	0.0777
4004	1.435	72.3286	0.3661	0.275	13.8609	0.0702
4005	1.683	84.7006	0.4512	0.443	22.2949	0.1188
4006	1.560	74.3211	0.4432	0.212	10.1000	0.0602
4007	1.822	86.4326	0.4578	0.400	18.9753	0.1005
4008	1.700	85.8586	0.4156	0.336	16.9697	0.0822
4009	1.820	86.9565	0.4906	0.305	14.5724	0.0822
4010	1.465	69.5962	0.4014	0.240	11.4014	0.0658
Mean	1.7386	83.55454	0.43918	0.3285	15.83035	0.08280
SD	0.2627	10.46241	0.04785	0.0752	3.64031	0.01725
N	10	10	10	10	10	10
%Diff	-6.4212	-3.24148	-1.29679	-10.5392	-7.64842	-5.51378

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)
	-	-	-	-	-	-
1501	234	1.879	0.8030	0.0436	2.3204	0.0186
1502	251	1.982	0.7896	0.0567	2.8607	0.0226
1503	242	1.905	0.7872	0.0821	4.3097	0.0339
1504	280	2.032	0.7257	0.0851	4.1880	0.0304
1505	269	2.112	0.7851	0.0610	2.8883	0.0227
1506	238	1.886	0.7924	0.0662	3.5101	0.0278
1507	252	2.024	0.8032	0.0420	2.0751	0.0167
1508	241	1.963	0.8145	0.0721	3.6729	0.0299
1509	195	1.835	0.9410	0.0686	3.7384	0.0352
1510	236	2.016	0.8542	0.0697	3.4573	0.0295
Mean	243.8	1.9634	0.80961	0.06471	3.30210	0.02673
SD	22.7	0.0860	0.05598	0.01435	0.74764	0.00629
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
1501	0.0150	0.7983	0.0064	0.0161	0.8568	0.0069
1502	0.0130	0.6559	0.0052	0.0079	0.3986	0.0031
1503	0.0121	0.6352	0.0050	0.0070	0.3675	0.0029
1504	0.0125	0.6152	0.0045	0.0108	0.5315	0.0039
1505	0.0158	0.7481	0.0059	0.0208	0.9848	0.0077
1506	0.0122	0.6469	0.0051	0.0159	0.8431	0.0067
1507	0.0148	0.7312	0.0059	0.0152	0.7510	0.0060
1508	0.0143	0.7285	0.0059	0.0139	0.7081	0.0058
1509	0.0120	0.6540	0.0062	0.0150	0.8174	0.0077
1510	0.0103	0.5109	0.0044	0.0138	0.6845	0.0058
Mean	0.01320	0.67241	0.00544	0.01364	0.69433	0.00565
SD	0.00171	0.08178	0.00071	0.00411	0.20342	0.00178
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
1501	0.651	34.6461	0.2782	1.386	73.7626	0.5923
1502	0.832	41.9778	0.3315	1.595	80.4743	0.6355
1503	0.808	42.4147	0.3339	1.600	83.9895	0.6612
1504	0.804	39.5669	0.2871	1.837	90.4035	0.6561
1505	0.781	36.9792	0.2903	1.581	74.8580	0.5877
1506	0.694	36.7975	0.2916	1.378	73.0647	0.5790
1507	0.717	35.4249	0.2845	1.567	77.4209	0.6218
1508	0.787	40.0917	0.3266	1.665	84.8192	0.6909
1509	0.758	41.3079	0.3887	1.483	80.8174	0.7605
1510	0.697	34.5734	0.2953	1.530	75.8929	0.6483
Mean	0.7529	38.37800	0.31078	1.5622	79.55030	0.64332
SD	0.0598	3.05079	0.03435	0.1339	5.60960	0.05463
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Ovary Paired (g)	Ovary Paired (%br)	Ovary Paired (%bw)
	-	-	-	-	-	-
1501	5.682	302.3949	2.4282	0.081	4.3108	0.0346
1502	6.248	315.2371	2.4892	0.117	5.9031	0.0466
1503	5.858	307.5066	2.4207	0.134	7.0341	0.0554
1504	7.340	361.2205	2.6214	0.113	5.5610	0.0404
1505	6.072	287.5000	2.2572	0.115	5.4451	0.0428
1506	6.090	322.9056	2.5588	0.099	5.2492	0.0416
1507	5.790	286.0672	2.2976	0.094	4.6443	0.0373
1508	6.814	347.1218	2.8274	0.113	5.7565	0.0469
1509	5.257	286.4850	2.6959	0.120	6.5395	0.0615
1510	5.708	283.1349	2.4186	0.095	4.7123	0.0403
Mean	6.0859	309.95736	2.50152	0.1081	5.51559	0.04473
SD	0.6020	27.10739	0.17695	0.0155	0.84961	0.00826
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Spleen (g)	Spleen (%br)	Spleen (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
1501	0.378	20.1171	0.1615	0.313	16.6578	0.1338
1502	0.464	23.4107	0.1849	0.314	15.8426	0.1251
1503	0.450	23.6220	0.1860	0.282	14.8031	0.1165
1504	0.727	35.7776	0.2596	0.343	16.8799	0.1225
1505	0.524	24.8106	0.1948	0.387	18.3239	0.1439
1506	0.451	23.9130	0.1895	0.277	14.6872	0.1164
1507	0.434	21.4427	0.1722	0.358	17.6877	0.1421
1508	0.594	30.2598	0.2465	0.287	14.6205	0.1191
1509	0.413	22.5068	0.2118	0.240	13.0790	0.1231
1510	0.416	20.6349	0.1763	0.315	15.6250	0.1335
Mean	0.4851	24.64953	0.19830	0.3116	15.82067	0.12758
SD	0.1048	4.83048	0.03198	0.0430	1.59481	0.01011
N	10	10	10	10	10	10

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights		
	Uterus/ Cervix (g)	Uterus/ Cervix (%br)	Uterus/ Cervix (%bw)
	-	-	-
1501	0.466	24.8004	0.1991
1502	0.403	20.3330	0.1606
1503	0.637	33.4383	0.2632
1504	0.663	32.6280	0.2368
1505	0.729	34.5170	0.2710
1506	0.445	23.5949	0.1870
1507	1.297	64.0810	0.5147
1508	0.549	27.9674	0.2278
1509	0.368	20.0545	0.1887
1510	0.439	21.7758	0.1860
Mean	0.5996	30.31904	0.24349
SD	0.2730	13.04618	0.10183
N	10	10	10

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)
	-	-	-	-	-	-
2501	235	1.947	0.8285	0.0523	2.6862	0.0223
2502	234	1.877	0.8021	0.0551	2.9355	0.0235
2503	274	1.904	0.6949	0.0661	3.4716	0.0241
2504	262	1.967	0.7508	0.0704	3.5791	0.0269
2505	249	1.984	0.7968	0.0603	3.0393	0.0242
2506	267	1.941	0.7270	0.0667	3.4364	0.0250
2507	237	1.957	0.8257	0.0478	2.4425	0.0202
2508	250	1.882	0.7528	0.0795	4.2242	0.0318
2509	260	1.979	0.7612	0.0563	2.8449	0.0217
2510	234	1.955	0.8355	0.0649	3.3197	0.0277
Mean	250.2	1.9393	0.77752	0.06194	3.19794	0.02474
SD	15.0	0.0385	0.04742	0.00944	0.51600	0.00337
N	10	10	10	10	10	10
%Diff	2.6	-1.2275	-3.96301	-4.28064	-3.15426	-7.47277

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Female Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
2501	0.0108	0.5547	0.0046	0.0176	0.9040	0.0075
2502	0.0110	0.5860	0.0047	0.0160	0.8524	0.0068
2503	0.0162	0.8508	0.0059	0.0135	0.7090	0.0049
2504	0.0069	0.3508	0.0026	0.0141	0.7168	0.0054
2505	0.0111	0.5595	0.0045	0.0104	0.5242	0.0042
2506	0.0120	0.6182	0.0045	0.0182	0.9377	0.0068
2507	0.0113	0.5774	0.0048	0.0113	0.5774	0.0048
2508	0.0122	0.6482	0.0049	0.0180	0.9564	0.0072
2509	0.0135	0.6822	0.0052	0.0129	0.6518	0.0050
2510	0.0084	0.4297	0.0036	0.0255	1.3043	0.0109
Mean	0.01134	0.58576	0.00452	0.01575	0.81341	0.00635
SD	0.00254	0.13574	0.00088	0.00440	0.22908	0.00198
N	10	10	10	10	10	10
%Diff	-14.09091	-12.88650	-16.83311	15.46921	17.15029	12.25222

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Female Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
2501	0.672	34.5146	0.2860	1.576	80.9450	0.6706
2502	0.687	36.6010	0.2936	1.455	77.5173	0.6218
2503	0.966	50.7353	0.3526	1.772	93.0672	0.6467
2504	0.879	44.6873	0.3355	1.820	92.5267	0.6947
2505	0.725	36.5423	0.2912	1.584	79.8387	0.6361
2506	0.858	44.2040	0.3213	1.748	90.0567	0.6547
2507	0.701	35.8201	0.2958	1.495	76.3924	0.6308
2508	0.757	40.2232	0.3028	1.701	90.3826	0.6804
2509	0.806	40.7276	0.3100	1.610	81.3542	0.6192
2510	0.680	34.7826	0.2906	1.689	86.3939	0.7218
Mean	0.7731	39.88381	0.30793	1.6450	84.84747	0.65769
SD	0.1004	5.30855	0.02206	0.1205	6.36341	0.03374
N	10	10	10	10	10	10
%Diff	2.6830	3.92362	-0.91655	5.3002	6.65890	2.23256

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Ovary Paired (g)	Ovary Paired (%br)	Ovary Paired (%bw)
	-	-	-	-	-	-
2501	6.132	314.9461	2.6094	0.083	4.2630	0.0353
2502	5.839	311.0815	2.4953	0.079	4.2088	0.0338
2503	7.025	368.9601	2.5639	0.146	7.6681	0.0533
2504	7.469	379.7153	2.8508	0.161	8.1851	0.0615
2505	5.965	300.6552	2.3956	0.113	5.6956	0.0454
2506	7.328	377.5374	2.7446	0.095	4.8944	0.0356
2507	5.773	294.9923	2.4359	0.133	6.7961	0.0561
2508	7.410	393.7301	2.9640	0.122	6.4825	0.0488
2509	6.031	304.7499	2.3196	0.106	5.3562	0.0408
2510	6.642	339.7442	2.8385	0.118	6.0358	0.0504
Mean	6.5614	338.61121	2.62174	0.1156	5.95855	0.04609
SD	0.6926	37.96635	0.21810	0.0264	1.34836	0.00956
N	10	10	10	10	10	10
%Diff	7.8131	9.24445	4.80600	6.9380	8.03101	3.04141

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights					
	Spleen (g)	Spleen (%br)	Spleen (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
2501	0.554	28.4540	0.2357	0.220	11.2994	0.0936
2502	0.442	23.5482	0.1889	0.246	13.1060	0.1051
2503	0.448	23.5294	0.1635	0.335	17.5945	0.1223
2504	0.521	26.4870	0.1989	0.342	17.3869	0.1305
2505	0.440	22.1774	0.1767	0.324	16.3306	0.1301
2506	0.558	28.7481	0.2090	0.271	13.9619	0.1015
2507	0.405	20.6949	0.1709	0.292	14.9208	0.1232
2508	0.482	25.6111	0.1928	0.267	14.1870	0.1068
2509	0.536	27.0844	0.2062	0.413	20.8691	0.1588
2510	0.420	21.4834	0.1795	0.359	18.3632	0.1534
Mean	0.4806	24.78179	0.19220	0.3069	15.80195	0.12254
SD	0.0574	2.89768	0.02136	0.0584	2.83925	0.02166
N	10	10	10	10	10	10
%Diff	-0.9276	0.53659	-3.07759	-1.5083	-0.11833	-3.95122

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

500 mg/kg /day Group 2	Organ Weights		
	Uterus/ Cervix (g)	Uterus/ Cervix (%br)	Uterus/ Cervix (%bw)
	-	-	-
2501	0.576	29.5840	0.2451
2502	1.115	59.4033	0.4765
2503	0.773	40.5987	0.2821
2504	0.451	22.9283	0.1721
2505	0.469	23.6391	0.1884
2506	0.952	49.0469	0.3566
2507	1.244	63.5667	0.5249
2508	0.411	21.8385	0.1644
2509	0.660	33.3502	0.2538
2510	0.542	27.7238	0.2316
Mean	0.7193	37.16794	0.28955
SD	0.2933	15.37045	0.12524
N	10	10	10
%Diff	19.9633	22.58947	18.91734

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)
	-	-	-	-	-	-
3501	259	2.048	0.7907	0.0834	4.0723	0.0322
3502	239	1.961	0.8205	0.0687	3.5033	0.0287
3503	251	1.896	0.7554	0.0615	3.2437	0.0245
3504	280	2.035	0.7268	0.0849	4.1720	0.0303
3505	258	1.903	0.7376	0.0615	3.2317	0.0238
3506	254	1.962	0.7724	0.0723	3.6850	0.0285
3507	279	1.920	0.6882	0.0554	2.8854	0.0199
3508	250	2.189	0.8756	0.0796	3.6364	0.0318
3509	242	2.015	0.8326	0.0708	3.5136	0.0293
3510	279	1.947	0.6978	0.0509	2.6143	0.0182
Mean	259.1	1.9876	0.76977	0.06890	3.45577	0.02673
SD	15.3	0.0884	0.06064	0.01160	0.48447	0.00489
N	10	10	10	10	10	10
%Diff	6.3	1.2326	-4.92043	6.47504	4.65379	-0.02322

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Female Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
3501	0.0147	0.7178	0.0057	0.0160	0.7813	0.0062
3502	0.0115	0.5864	0.0048	0.0229	1.1678	0.0096
3503	0.0144	0.7595	0.0057	0.0182	0.9599	0.0073
3504	0.0155	0.7617	0.0055	0.0171	0.8403	0.0061
3505	0.0115	0.6043	0.0045	0.0153	0.8040	0.0059
3506	0.0134	0.6830	0.0053	0.0257	1.3099	0.0101
3507	0.0110	0.5729	0.0039	0.0155	0.8073	0.0056
3508	0.0130	0.5939	0.0052	0.0150	0.6852	0.0060
3509	0.0106	0.5261	0.0044	0.0126	0.6253	0.0052
3510	0.0125	0.6420	0.0045	0.0126	0.6471	0.0045
Mean	0.01281	0.64475	0.00495	0.01709	0.86281	0.00664
SD	0.00168	0.08200	0.00062	0.00423	0.22372	0.00183
N	10	10	10	10	10	10
%Diff	-2.95455	-4.11283	-8.97810	25.29326	24.26473	17.53834

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Female Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
3501	0.721	35.2051	0.2784	1.657	80.9082	0.6398
3502	0.748	38.1438	0.3130	1.781	90.8210	0.7452
3503	0.853	44.9895	0.3398	1.736	91.5612	0.6916
3504	0.858	42.1622	0.3064	1.983	97.4447	0.7082
3505	0.817	42.9322	0.3167	1.970	103.5208	0.7636
3506	0.772	39.3476	0.3039	2.016	102.7523	0.7937
3507	0.717	37.3438	0.2570	1.743	90.7813	0.6247
3508	0.878	40.1096	0.3512	1.890	86.3408	0.7560
3509	0.687	34.0943	0.2839	1.636	81.1911	0.6760
3510	0.803	41.2429	0.2878	1.706	87.6220	0.6115
Mean	0.7854	39.55709	0.30381	1.8118	91.29433	0.70103
SD	0.0665	3.44090	0.02846	0.1413	7.93815	0.06310
N	10	10	10	10	10	10
%Diff	4.3166	3.07230	-2.24164	15.9775	14.76302	8.97017

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Ovary Paired (g)	Ovary Paired (%br)	Ovary Paired (%bw)
	-	-	-	-	-	-
3501	8.210	400.8789	3.1699	0.120	5.8594	0.0463
3502	6.485	330.6986	2.7134	0.085	4.3345	0.0356
3503	6.704	353.5865	2.6709	0.136	7.1730	0.0542
3504	6.983	343.1450	2.4939	0.150	7.3710	0.0536
3505	7.517	395.0079	2.9136	0.100	5.2549	0.0388
3506	6.689	340.9276	2.6335	0.110	5.6065	0.0433
3507	7.082	368.8542	2.5384	0.089	4.6354	0.0319
3508	7.049	322.0192	2.8196	0.137	6.2586	0.0548
3509	6.507	322.9280	2.6888	0.152	7.5434	0.0628
3510	7.382	379.1474	2.6459	0.120	6.1633	0.0430
Mean	7.0608	355.71933	2.72878	0.1199	6.02000	0.04642
SD	0.5315	28.91143	0.19707	0.0239	1.11021	0.00977
N	10	10	10	10	10	10
%Diff	16.0190	14.76396	9.08515	10.9158	9.14514	3.78971

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights					
	Spleen (g)	Spleen (%br)	Spleen (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
3501	0.488	23.8281	0.1884	0.254	12.4023	0.0981
3502	0.540	27.5370	0.2259	0.366	18.6639	0.1531
3503	0.520	27.4262	0.2072	0.404	21.3080	0.1610
3504	0.629	30.9091	0.2246	0.404	19.8526	0.1443
3505	0.624	32.7903	0.2419	0.332	17.4461	0.1287
3506	0.500	25.4842	0.1969	0.315	16.0550	0.1240
3507	0.476	24.7917	0.1706	0.289	15.0521	0.1036
3508	0.768	35.0845	0.3072	0.255	11.6492	0.1020
3509	0.437	21.6873	0.1806	0.228	11.3151	0.0942
3510	0.484	24.8588	0.1735	0.386	19.8254	0.1384
Mean	0.5466	27.43972	0.21167	0.3233	16.35698	0.12473
SD	0.0995	4.25244	0.04123	0.0655	3.65585	0.02429
N	10	10	10	10	10	10
%Diff	12.6778	11.31945	6.74231	3.7548	3.38993	-2.23745

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

1000 mg/kg /day Group 3	Organ Weights		
	Uterus/ Cervix (g)	Uterus/ Cervix (%br)	Uterus/ Cervix (%bw)
	-	-	-
3501	0.607	29.6387	0.2344
3502	0.585	29.8317	0.2448
3503	0.420	22.1519	0.1673
3504	0.678	33.3170	0.2421
3505	0.825	43.3526	0.3198
3506	0.538	27.4210	0.2118
3507	0.440	22.9167	0.1577
3508	0.531	24.2577	0.2124
3509	0.460	22.8288	0.1901
3510	1.139	58.5003	0.4082
Mean	0.6223	31.42162	0.23886
SD	0.2183	11.47135	0.07514
N	10	10	10
%Diff	3.7859	3.63661	-1.90116

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)
	-	-	-	-	-	-
4501	247	2.010	0.8138	0.0764	3.8010	0.0309
4502	239	1.952	0.8167	0.0567	2.9047	0.0237
4503	227	1.932	0.8511	0.0610	3.1573	0.0269
4504	234	1.851	0.7910	0.0561	3.0308	0.0240
4505	267	1.924	0.7206	0.0615	3.1965	0.0230
4506	234	1.972	0.8427	0.0659	3.3418	0.0282
4507	260	1.978	0.7608	0.0675	3.4125	0.0260
4508	299	1.885	0.6304	0.0607	3.2202	0.0203
4509	246	1.827	0.7427	0.0760	4.1598	0.0309
4510	261	1.953	0.7483	0.0731	3.7430	0.0280
Mean	251.4	1.9284	0.77181	0.06549	3.39676	0.02619
SD	21.3	0.0581	0.06633	0.00757	0.39065	0.00346
N	10	10	10	10	10	10
%Diff	3.1	-1.7826	-4.66818	1.20538	2.86669	-2.04509

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
4501	0.0121	0.6020	0.0049	0.0186	0.9254	0.0075
4502	0.0131	0.6711	0.0055	0.0132	0.6762	0.0055
4503	0.0113	0.5849	0.0050	0.0200	1.0352	0.0088
4504	0.0122	0.6591	0.0052	0.0180	0.9724	0.0077
4505	0.0169	0.8784	0.0063	0.0103	0.5353	0.0039
4506	0.0112	0.5680	0.0048	0.0118	0.5984	0.0050
4507	0.0154	0.7786	0.0059	0.0193	0.9757	0.0074
4508	0.0152	0.8064	0.0051	0.0212	1.1247	0.0071
4509	0.0136	0.7444	0.0055	0.0183	1.0016	0.0074
4510	0.0149	0.7629	0.0057	0.0153	0.7834	0.0059
Mean	0.01359	0.70557	0.00539	0.01660	0.86284	0.00663
SD	0.00194	0.10420	0.00049	0.00372	0.20125	0.00150
N	10	10	10	10	10	10
%Diff	2.95455	4.93143	-0.82181	21.70088	24.26921	17.23260

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
4501	0.816	40.5970	0.3304	2.193	109.1045	0.8879
4502	0.807	41.3422	0.3377	1.656	84.8361	0.6929
4503	0.727	37.6294	0.3203	1.712	88.6128	0.7542
4504	0.679	36.6829	0.2902	1.684	90.9778	0.7197
4505	0.835	43.3992	0.3127	1.849	96.1019	0.6925
4506	0.757	38.3874	0.3235	1.968	99.7972	0.8410
4507	0.822	41.5571	0.3162	1.907	96.4105	0.7335
4508	0.883	46.8435	0.2953	2.061	109.3369	0.6893
4509	0.813	44.4992	0.3305	1.909	104.4882	0.7760
4510	0.828	42.3963	0.3172	1.896	97.0814	0.7264
Mean	0.7967	41.33342	0.31739	1.8835	97.67473	0.75133
SD	0.0592	3.16928	0.01508	0.1693	8.25829	0.06664
N	10	10	10	10	10	10
%Diff	5.8175	7.70081	2.12761	20.5671	22.78361	16.78936

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Individual Organ Weights: Days 91/92

(b) (4)
Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Ovary Paired (g)	Ovary Paired (%br)	Ovary Paired (%bw)
	-	-	-	-	-	-
4501	7.409	368.6070	2.9996	0.125	6.2189	0.0506
4502	7.258	371.8238	3.0368	0.124	6.3525	0.0519
4503	6.376	330.0207	2.8088	0.118	6.1077	0.0520
4504	7.031	379.8487	3.0047	0.125	6.7531	0.0534
4505	7.916	411.4345	2.9648	0.119	6.1850	0.0446
4506	6.799	344.7769	2.9056	0.117	5.9331	0.0500
4507	8.092	409.1001	3.1123	0.137	6.9262	0.0527
4508	8.102	429.8143	2.7097	0.193	10.2387	0.0645
4509	7.062	386.5353	2.8707	0.120	6.5681	0.0488
4510	7.037	360.3175	2.6962	0.111	5.6836	0.0425
Mean	7.3082	379.22787	2.91092	0.1289	6.69668	0.05110
SD	0.5741	31.04805	0.13930	0.0235	1.29887	0.00590
N	10	10	10	10	10	10
%Diff	20.0841	22.34840	16.36618	19.2414	21.41368	14.24650

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Spleen (g)	Spleen (%br)	Spleen (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
4501	0.577	28.7065	0.2336	0.383	19.0547	0.1551
4502	0.526	26.9467	0.2201	0.346	17.7254	0.1448
4503	0.458	23.7060	0.2018	0.238	12.3188	0.1048
4504	0.442	23.8790	0.1889	0.278	15.0189	0.1188
4505	0.542	28.1705	0.2030	0.291	15.1247	0.1090
4506	0.601	30.4767	0.2568	0.313	15.8722	0.1338
4507	0.661	33.4176	0.2542	0.459	23.2053	0.1765
4508	0.690	36.6048	0.2308	0.357	18.9390	0.1194
4509	0.441	24.1379	0.1793	0.357	19.5402	0.1451
4510	0.664	33.9990	0.2544	0.330	16.8971	0.1264
Mean	0.5602	29.00446	0.22228	0.3352	17.36964	0.13337
SD	0.0942	4.56312	0.02830	0.0613	3.03199	0.02228
N	10	10	10	10	10	10
%Diff	15.4813	17.66742	12.09258	7.5738	9.79078	4.53664

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Individual Organ Weights: Days 91/92

(b) (4)

Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights		
	Uterus/ Cervix (g)	Uterus/ Cervix (%br)	Uterus/ Cervix (%bw)
	-	-	-
4501	0.801	39.8507	0.3243
4502	0.552	28.2787	0.2310
4503	0.515	26.6563	0.2269
4504	0.563	30.4160	0.2406
4505	0.580	30.1455	0.2172
4506	1.040	52.7383	0.4444
4507	0.611	30.8898	0.2350
4508	0.455	24.1379	0.1522
4509	0.513	28.0788	0.2085
4510	0.426	21.8126	0.1632
Mean	0.6056	31.30047	0.24433
SD	0.1838	8.92795	0.08440
N	10	10	10
%Diff	1.0007	3.23703	0.34570

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Epididymis (Paired) (g)	Epididymis (Paired) (%br)	Epididymis (Paired) (%bw)
	-	-	-	-	-	-
1011	451	2.226	0.4936	1.878	84.3666	0.4164
1012	414	2.167	0.5234	1.694	78.1726	0.4092
1013	434	2.198	0.5065	1.654	75.2502	0.3811
1014	448	2.293	0.5118	1.627	70.9551	0.3632
1015	394	2.102	0.5335	1.459	69.4101	0.3703
Mean	428.2	2.1972	0.51376	1.6624	75.63091	0.38803
SD	24.1	0.0707	0.01540	0.1501	5.98914	0.02363
N	5	5	5	5	5	5

Sponsor Reference No. (b) (4)

Test Facility Study No. (b) (4)

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Individual Organ Weights: Day 120

(b) (4)

Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Epididymis Left (g)	Epididymis Left (%br)	Epididymis Left (%bw)	Epididymis Right (g)	Epididymis Right (%br)	Epididymis Right (%bw)
	-	-	-	-	-	-
1011	0.936	42.0485	0.2075	0.942	42.3181	0.2089
1012	0.879	40.5630	0.2123	0.815	37.6096	0.1969
1013	0.795	36.1692	0.1832	0.859	39.0810	0.1979
1014	0.792	34.5399	0.1768	0.835	36.4152	0.1864
1015	0.716	34.0628	0.1817	0.743	35.3473	0.1886
Mean	0.8236	37.47669	0.19231	0.8388	38.15422	0.19572
SD	0.0853	3.61993	0.01635	0.0721	2.71091	0.00891
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Epididymis Cauda, Left (g)	Epididymis Cauda, Left (%br)	Epididymis Cauda, Left (%bw)	Seminal Ves/ Coagulating (g)	Seminal Ves/ Coagul (%br)	Seminal Ves/ Coagul (%bw)
	-	-	-	-	-	-
1011	0.3999	17.9650	0.0887	1.827	82.0755	0.4051
1012	0.3658	16.8805	0.0884	2.294	105.8606	0.5541
1013	0.3405	15.4914	0.0785	1.350	61.4195	0.3111
1014	0.3349	14.6053	0.0748	1.769	77.1478	0.3949
1015	0.3155	15.0095	0.0801	1.132	53.8535	0.2873
Mean	0.35132	15.99033	0.08206	1.6744	76.07138	0.39049
SD	0.03256	1.39828	0.00620	0.4515	20.20471	0.10483
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)
	-	-	-	-	-	-
1011	0.0688	3.0907	0.0153	0.0081	0.3639	0.0018
1012	0.0749	3.4564	0.0181	0.0115	0.5307	0.0028
1013	0.0628	2.8571	0.0145	0.0092	0.4186	0.0021
1014	0.0931	4.0602	0.0208	0.0105	0.4579	0.0023
1015	0.0501	2.3834	0.0127	0.0107	0.5090	0.0027
Mean	0.06994	3.16958	0.01626	0.01000	0.45602	0.00235
SD	0.01587	0.63192	0.00318	0.00135	0.06761	0.00041
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Gland Prostate (g)	Gland Prostate (%br)	Gland Prostate (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
1011	1.186	53.2794	0.2630	0.0186	0.8356	0.0041
1012	1.154	53.2533	0.2787	0.0148	0.6830	0.0036
1013	1.015	46.1783	0.2339	0.0193	0.8781	0.0044
1014	1.157	50.4579	0.2583	0.0231	1.0074	0.0052
1015	0.732	34.8240	0.1858	0.0140	0.6660	0.0036
Mean	1.0488	47.59860	0.24393	0.01796	0.81401	0.00417
SD	0.1891	7.70765	0.03627	0.00368	0.14234	0.00067
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
1011	1.274	57.2327	0.2825	2.571	115.4987	0.5701
1012	1.189	54.8685	0.2872	2.603	120.1200	0.6287
1013	1.247	56.7334	0.2873	2.226	101.2739	0.5129
1014	1.273	55.5168	0.2842	2.900	126.4719	0.6473
1015	1.058	50.3330	0.2685	2.251	107.0885	0.5713
Mean	1.2082	54.93688	0.28194	2.5102	114.09058	0.58607
SD	0.0908	2.74020	0.00777	0.2794	10.06143	0.05339
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Spleen (g)	Spleen (%br)	Spleen (%bw)
	-	-	-	-	-	-
1011	11.117	499.4160	2.4650	0.738	33.1536	0.1636
1012	11.362	524.3193	2.7444	0.655	30.2261	0.1582
1013	9.714	441.9472	2.2382	0.870	39.5814	0.2005
1014	11.420	498.0375	2.5491	0.814	35.4993	0.1817
1015	8.817	419.4577	2.2378	0.602	28.6394	0.1528
Mean	10.4860	476.63554	2.44692	0.7358	33.41999	0.17136
SD	1.1640	43.94123	0.21596	0.1102	4.34203	0.01956
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Testis (Paired) (g)	Testis (Paired) (%br)	Testis (Paired) (%bw)	Testis Left (g)	Testis Left (%br)	Testis Left (%bw)
	-	-	-	-	-	-
1011	4.103	184.3217	0.9098	2.023	90.8805	0.4486
1012	3.867	178.4495	0.9341	1.985	91.6013	0.4795
1013	3.804	173.0664	0.8765	1.865	84.8499	0.4297
1014	4.276	186.4806	0.9545	2.217	96.6856	0.4949
1015	4.226	201.0466	1.0726	2.107	100.2379	0.5348
Mean	4.0552	184.67295	0.94947	2.0394	92.85102	0.47748
SD	0.2114	10.54670	0.07470	0.1321	5.88924	0.04094
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Testis Right (g)	Testis Right (%br)	Testis Right (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
1011	2.080	93.4412	0.4612	0.270	12.1294	0.0599
1012	1.882	86.8482	0.4546	0.263	12.1366	0.0635
1013	1.939	88.2166	0.4468	0.409	18.6078	0.0942
1014	2.059	89.7950	0.4596	0.269	11.7314	0.0600
1015	2.119	100.8088	0.5378	0.281	13.3682	0.0713
Mean	2.0158	91.82193	0.47200	0.2984	13.59468	0.06980
SD	0.1005	5.59531	0.03722	0.0622	2.86915	0.01443
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Epididymis (Paired) (g)	Epididymis (Paired) (%br)	Epididymis (Paired) (%bw)
	-	-	-	-	-	-
4011	402	1.924	0.4786	1.460	75.8836	0.3632
4012	384	2.009	0.5232	1.453	72.3245	0.3784
4013	440	2.232	0.5073	1.414	63.3513	0.3214
4014	412	2.132	0.5175	1.551	72.7486	0.3765
4015	368	2.178	0.5918	1.353	62.1212	0.3677
Mean	401.2	2.0950	0.52368	1.4462	69.28583	0.36141
SD	27.5	0.1262	0.04179	0.0724	6.15032	0.02324
N	5	5	5	5	5	5
%Diff	-6.3	-4.6514	1.93072	-13.0053	-8.38953	-6.86098

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Epididymis Left (g)	Epididymis Left (%br)	Epididymis Left (%bw)	Epididymis Right (g)	Epididymis Right (%br)	Epididymis Right (%bw)
	-	-	-	-	-	-
4011	0.699	36.3306	0.1739	0.761	39.5530	0.1893
4012	0.736	36.6351	0.1917	0.717	35.6894	0.1867
4013	0.697	31.2276	0.1584	0.717	32.1237	0.1630
4014	0.748	35.0844	0.1816	0.803	37.6642	0.1949
4015	0.685	31.4509	0.1861	0.668	30.6703	0.1815
Mean	0.7130	34.14572	0.17833	0.7332	35.14011	0.18308
SD	0.0273	2.62819	0.01290	0.0510	3.71565	0.01224
N	5	5	5	5	5	5
%Diff	-13.4288	-8.88811	-7.26930	-12.5894	-7.89980	-6.45978

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Epididymis Cauda, Left (g)	Epididymis Cauda, Left (%br)	Epididymis Cauda, Left (%bw)	Seminal Ves/ Coagulating (g)	Seminal Ves/ Coagul (%br)	Seminal Ves/ Coagul (%bw)
	-	-	-	-	-	-
4011	0.3015	15.6705	0.0750	1.623	84.3555	0.4037
4012	0.2854	14.2061	0.0743	1.260	62.7178	0.3281
4013	0.2927	13.1138	0.0665	1.818	81.4516	0.4132
4014	0.3448	16.1726	0.0837	1.447	67.8705	0.3512
4015	0.2981	13.6869	0.0810	1.547	71.0285	0.4204
Mean	0.30450	14.56997	0.07611	1.5390	73.48478	0.38333
SD	0.02334	1.30502	0.00667	0.2069	9.15321	0.04111
N	5	5	5	5	5	5
%Diff	-13.32688	-8.88263	-7.25628	-8.0865	-3.40023	-1.83409

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)
	-	-	-	-	-	-
4011	0.0582	3.0249	0.0145	0.0083	0.4314	0.0021
4012	0.0532	2.6481	0.0139	0.0070	0.3484	0.0018
4013	0.0661	2.9615	0.0150	0.0103	0.4615	0.0023
4014	0.0555	2.6032	0.0135	0.0094	0.4409	0.0023
4015	0.0542	2.4885	0.0147	0.0100	0.4591	0.0027
Mean	0.05744	2.74524	0.01431	0.00900	0.42827	0.00225
SD	0.00519	0.23479	0.00064	0.00135	0.04636	0.00033
N	5	5	5	5	5	5
%Diff	-17.87246	-13.38786	-12.00309	-10.00000	-6.08546	-4.47237

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Gland Prostate (g)	Gland Prostate (%br)	Gland Prostate (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
4011	0.795	41.3202	0.1978	0.0179	0.9304	0.0045
4012	0.877	43.6536	0.2284	0.0207	1.0304	0.0054
4013	0.842	37.7240	0.1914	0.0188	0.8423	0.0043
4014	1.198	56.1914	0.2908	0.0188	0.8818	0.0046
4015	0.769	35.3076	0.2090	0.0182	0.8356	0.0049
Mean	0.8962	42.83935	0.22345	0.01888	0.90409	0.00472
SD	0.1738	8.12621	0.04018	0.00109	0.08006	0.00045
N	5	5	5	5	5	5
%Diff	-14.5500	-9.99873	-8.39413	5.12249	11.06547	13.27819

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
4011	1.152	59.8753	0.2866	2.411	125.3119	0.5998
4012	0.982	48.8800	0.2557	1.997	99.4027	0.5201
4013	1.154	51.7025	0.2623	2.728	122.2222	0.6200
4014	1.054	49.4371	0.2558	2.948	138.2739	0.7155
4015	0.941	43.2048	0.2557	2.293	105.2801	0.6231
Mean	1.0566	50.61995	0.26322	2.4754	118.09815	0.61569
SD	0.0969	6.04657	0.01335	0.3720	15.73158	0.06972
N	5	5	5	5	5	5
%Diff	-12.5476	-7.85798	-6.63888	-1.3863	3.51263	5.05332

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Spleen (g)	Spleen (%br)	Spleen (%bw)
	-	-	-	-	-	-
4011	9.850	511.9543	2.4502	0.642	33.3680	0.1597
4012	8.551	425.6346	2.2268	0.763	37.9791	0.1987
4013	10.313	462.0520	2.3439	0.663	29.7043	0.1507
4014	9.979	468.0582	2.4221	0.711	33.3490	0.1726
4015	8.830	405.4178	2.3995	0.697	32.0018	0.1894
Mean	9.5046	454.62337	2.36850	0.6952	33.28044	0.17421
SD	0.7685	41.18265	0.08831	0.0467	3.02131	0.01998
N	5	5	5	5	5	5
%Diff	-9.3591	-4.61824	-3.20489	-5.5178	-0.41756	1.66412

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Testis (Paired) (g)	Testis (Paired) (%br)	Testis (Paired) (%bw)	Testis Left (g)	Testis Left (%br)	Testis Left (%bw)
	-	-	-	-	-	-
4011	3.451	179.3659	0.8585	1.744	90.6445	0.4338
4012	3.406	169.5371	0.8870	1.714	85.3161	0.4464
4013	3.719	166.6219	0.8452	1.882	84.3190	0.4277
4014	4.185	196.2946	1.0158	2.115	99.2026	0.5133
4015	3.389	155.6015	0.9209	1.668	76.5840	0.4533
Mean	3.6300	173.48418	0.90547	1.8246	87.21324	0.45490
SD	0.3377	15.30825	0.06817	0.1809	8.37369	0.03418
N	5	5	5	5	5	5
%Diff	-10.4853	-6.05870	-4.63415	-10.5325	-6.07185	-4.72759

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Individual Organ Weights: Day 120

(b) (4)
Sex: Male Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Testis Right (g)	Testis Right (%br)	Testis Right (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
4011	1.707	88.7214	0.4246	0.401	20.8420	0.0998
4012	1.692	84.2210	0.4406	0.243	12.0956	0.0633
4013	1.837	82.3029	0.4175	0.349	15.6362	0.0793
4014	2.070	97.0919	0.5024	0.237	11.1163	0.0575
4015	1.721	79.0174	0.4677	0.229	10.5142	0.0622
Mean	1.8054	86.27093	0.45057	0.2918	14.04086	0.07242
SD	0.1586	6.99392	0.03481	0.0783	4.28879	0.01735
N	5	5	5	5	5	5
%Diff	-10.4375	-6.04540	-4.53963	-2.2118	3.28209	3.75521

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Individual Organ Weights: Day 120

(b) (4)
Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)
	-	-	-	-	-	-
1511	246	1.863	0.7573	0.0731	3.9238	0.0297
1512	252	2.000	0.7937	0.0512	2.5600	0.0203
1513	292	1.888	0.6466	0.0587	3.1091	0.0201
1514	241	1.964	0.8149	0.0667	3.3961	0.0277
1515	278	2.138	0.7691	0.0787	3.6810	0.0283
Mean	261.8	1.9706	0.75631	0.06568	3.33401	0.02522
SD	22.1	0.1088	0.06526	0.01100	0.52957	0.00464
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
1511	0.0125	0.6710	0.0051	0.0221	1.1863	0.0090
1512	0.0151	0.7550	0.0060	0.0193	0.9650	0.0077
1513	0.0147	0.7786	0.0050	0.0190	1.0064	0.0065
1514	0.0119	0.6059	0.0049	0.0111	0.5652	0.0046
1515	0.0152	0.7109	0.0055	0.0193	0.9027	0.0069
Mean	0.01388	0.70428	0.00530	0.01816	0.92510	0.00694
SD	0.00156	0.06879	0.00043	0.00414	0.22718	0.00161
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
1511	0.760	40.7944	0.3089	1.507	80.8910	0.6126
1512	0.788	39.4000	0.3127	1.623	81.1500	0.6440
1513	0.933	49.4174	0.3195	1.662	88.0297	0.5692
1514	0.778	39.6130	0.3228	1.684	85.7434	0.6988
1515	0.833	38.9616	0.2996	1.985	92.8438	0.7140
Mean	0.8184	41.63729	0.31272	1.6922	85.73157	0.64772
SD	0.0695	4.40177	0.00913	0.1773	5.00716	0.06004
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Ovary Paired (g)	Ovary Paired (%br)	Ovary Paired (%bw)
	-	-	-	-	-	-
1511	6.435	345.4106	2.6159	0.116	6.2265	0.0472
1512	6.474	323.7000	2.5690	0.107	5.3500	0.0425
1513	6.434	340.7839	2.2034	0.122	6.4619	0.0418
1514	5.906	300.7128	2.4506	0.138	7.0265	0.0573
1515	6.351	297.0533	2.2845	0.091	4.2563	0.0327
Mean	6.3200	321.53214	2.42470	0.1148	5.86423	0.04428
SD	0.2357	22.23830	0.17794	0.0175	1.08271	0.00894
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights					
	Spleen (g)	Spleen (%br)	Spleen (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
1511	0.468	25.1208	0.1902	0.305	16.3714	0.1240
1512	0.462	23.1000	0.1833	0.314	15.7000	0.1246
1513	0.436	23.0932	0.1493	0.282	14.9364	0.0966
1514	0.386	19.6538	0.1602	0.293	14.9185	0.1216
1515	0.546	25.5379	0.1964	0.219	10.2432	0.0788
Mean	0.4596	23.30113	0.17589	0.2826	14.43393	0.10910
SD	0.0581	2.32922	0.02022	0.0376	2.41900	0.02058
N	5	5	5	5	5	5

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Individual Organ Weights: Day 120

(b) (4)

Sex: Female Day(s) Relative to Start Date

0 mg/kg /day Group 1	Organ Weights		
	Uterus/ Cervix (g)	Uterus/ Cervix (%br)	Uterus/ Cervix (%bw)
	-	-	-
1511	0.618	33.1723	0.2512
1512	0.988	49.4000	0.3921
1513	0.535	28.3369	0.1832
1514	0.449	22.8615	0.1863
1515	0.915	42.7970	0.3291
Mean	0.7010	35.31354	0.26839
SD	0.2378	10.75573	0.09120
N	5	5	5

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Individual Organ Weights: Day 120

(b) (4)
Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Terminal Body Wt (g)	Brain (g)	Brain (%bw)	Gland Adrenal (g)	Gland Adrenal (%br)	Gland Adrenal (%bw)
	-	-	-	-	-	-
4511	258	2.042	0.7915	0.0672	3.2909	0.0260
4512	247	1.944	0.7870	0.0664	3.4156	0.0269
4513	237	1.812	0.7646	0.1038	5.7285	0.0438
4514	272	2.016	0.7412	0.0798	3.9583	0.0293
4515	237	1.891	0.7979	0.0576	3.0460	0.0243
Mean	250.2	1.9410	0.77643	0.07496	3.88787	0.03007
SD	15.0	0.0935	0.02336	0.01796	1.08177	0.00788
N	5	5	5	5	5	5
%Diff	-4.4	-1.5021	2.66017	14.12911	16.61255	19.22534

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Individual Organ Weights: Day 120

(b) (4)
Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Gland Pituitary (g)	Gland Pituitary (%br)	Gland Pituitary (%bw)	Thyroid/ Parathyroid (g)	Thyroid/ Parathyroid (%br)	Thyroid/ Parathyroid (%bw)
	-	-	-	-	-	-
4511	0.0118	0.5779	0.0046	0.0157	0.7689	0.0061
4512	0.0139	0.7150	0.0056	0.0159	0.8179	0.0064
4513	0.0120	0.6623	0.0051	0.0148	0.8168	0.0062
4514	0.0131	0.6498	0.0048	0.0182	0.9028	0.0067
4515	0.0092	0.4865	0.0039	0.0162	0.8567	0.0068
Mean	0.01200	0.61829	0.00479	0.01616	0.83260	0.00646
SD	0.00178	0.08843	0.00064	0.00125	0.05009	0.00031
N	5	5	5	5	5	5
%Diff	-13.54467	-12.20987	-9.61980	-11.01322	-9.99894	-6.92761

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Individual Organ Weights: Day 120

(b) (4)
Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Heart (g)	Heart (%br)	Heart (%bw)	Kidney (g)	Kidney (%br)	Kidney (%bw)
	-	-	-	-	-	-
4511	0.722	35.3575	0.2798	1.852	90.6954	0.7178
4512	0.771	39.6605	0.3121	1.659	85.3395	0.6717
4513	0.761	41.9978	0.3211	1.764	97.3510	0.7443
4514	0.780	38.6905	0.2868	1.638	81.2500	0.6022
4515	0.748	39.5558	0.3156	1.759	93.0196	0.7422
Mean	0.7564	39.05241	0.30309	1.7344	89.53109	0.69564
SD	0.0226	2.40218	0.01851	0.0870	6.34078	0.05986
N	5	5	5	5	5	5
%Diff	-7.5758	-6.20810	-3.08000	2.4938	4.43188	7.39767

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Individual Organ Weights: Day 120

(b) (4)
Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Liver (g)	Liver (%br)	Liver (%bw)	Ovary Paired (g)	Ovary Paired (%br)	Ovary Paired (%bw)
	-	-	-	-	-	-
4511	6.626	324.4858	2.5682	0.109	5.3379	0.0422
4512	6.384	328.3951	2.5846	0.106	5.4527	0.0429
4513	6.781	374.2274	2.8612	0.119	6.5673	0.0502
4514	6.206	307.8373	2.2816	0.116	5.7540	0.0426
4515	6.873	363.4585	2.9000	0.103	5.4469	0.0435
Mean	6.5740	339.68080	2.63913	0.1106	5.71175	0.04430
SD	0.2768	27.97815	0.25158	0.0067	0.50270	0.00334
N	5	5	5	5	5	5
%Diff	4.0190	5.64443	8.84359	-3.6585	-2.60031	0.04072

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Individual Organ Weights: Day 120

(b) (4)
Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights					
	Spleen (g)	Spleen (%br)	Spleen (%bw)	Thymus (g)	Thymus (%br)	Thymus (%bw)
	-	-	-	-	-	-
4511	0.582	28.5015	0.2256	0.282	13.8100	0.1093
4512	0.502	25.8230	0.2032	0.251	12.9115	0.1016
4513	0.482	26.6004	0.2034	0.218	12.0309	0.0920
4514	0.525	26.0417	0.1930	0.355	17.6091	0.1305
4515	0.647	34.2147	0.2730	0.240	12.6917	0.1013
Mean	0.5476	28.23626	0.21964	0.2692	13.81065	0.10694
SD	0.0670	3.50456	0.03211	0.0532	2.21678	0.01454
N	5	5	5	5	5	5
%Diff	19.1471	21.17981	24.87263	-4.7417	-4.31815	-1.98538

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Individual Organ Weights: Day 120

(b) (4)
Sex: Female Day(s) Relative to Start Date

2000 mg/kg /day Group 4	Organ Weights		
	Uterus/ Cervix (g)	Uterus/ Cervix (%br)	Uterus/ Cervix (%bw)
	-	-	-
4511	1.095	53.6239	0.4244
4512	0.885	45.5247	0.3583
4513	0.637	35.1545	0.2688
4514	0.627	31.1012	0.2305
4515	0.615	32.5225	0.2595
Mean	0.7718	39.58536	0.30830
SD	0.2127	9.66765	0.08059
N	5	5	5
%Diff	10.0999	12.09683	14.87072

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1001	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

Animal: 1002	Group: 1		Sex: Male
Species: Rat	Strain: Han Wistar		
	Dose: 0 mg/kg /day		
	Removal Reason: Terminal Euthanasia		
	Study Day (Week) of Death: 91 (13)		
		Gross Status:	Complete
		Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

PANCREAS : Discoloration, pale (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
LIVER : Infiltration, mononuclear cell; multifocal, minimal
PANCREAS : Basophilic granules; decreased, diffuse, minimal [PANCREAS : Discoloration, pale (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

Animal:	1003	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; multifocal, minimal

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

Animal: 1004	Group: 1		Sex: Male
Species: Rat	Strain: Han Wistar		
	Dose: 0 mg/kg /day		
	Removal Reason: Terminal Euthanasia		
	Study Day (Week) of Death: 91 (13)		
		Gross Status:	Complete
		Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

LIVER : Focus, pale; right, focal, medial lobe (TGL)
STOMACH : Focus, dark; focal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

KIDNEY : Dilatation; unilateral, mild, pelvis
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
STOMACH : Hemorrhage; multifocal, minimal, glandular [STOMACH : Focus, dark; focal, glandular (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus, pale; right, focal, medial lobe (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1005	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; multifocal, minimal
LUNG : Inflammation, mixed cell; perivascular, multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1006	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
LIVER : Hyperplasia; focal, minimal, bile duct

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1007	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

GLAND, PITUITARY : (Comment) Damaged At Necropsy.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1008	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
GLAND, PITUITARY : Cyst; single, minimal, pars distalis
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
TONGUE : Hemorrhage; focal, minimal

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1009	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; multifocal, minimal

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1010	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

KIDNEY : Basophilia; tubular, unilateral, multifocal, minimal
KIDNEY : Dilatation; unilateral, mild, pelvis

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

GLAND, MAMMARY Not Present In Section.

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1011	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

GLAND, THYROID : (Comment) right Damaged At Necropsy.
TESTIS, RIGHT : (Comment) Damaged At Necropsy.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1012	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

TESTIS, RIGHT : (Comment) Damaged At Necropsy.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1013	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1014	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

EPIDIDYMIS, RIGHT : (Comment) Damaged At Necropsy.
KIDNEY : (Comment) Right; Damaged At Necropsy.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1015	Group:	1	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

LARGE INTESTINE, RECTUM : (Comment) Damaged At Necropsy.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1501	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

BRAIN : (Comment) Damaged At Necropsy.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; multifocal, minimal
THYMUS : Apoptosis, increased; minimal
VAGINA : Diestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1502	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
VAGINA : Metestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1503	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
VAGINA : Estrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1504	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
LIVER : Infiltration, mononuclear cell; multifocal, minimal
VAGINA : Diestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1505	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

HEART : Infiltration, mononuclear cell; myocardial, focal, minimal
KIDNEY : Inflammation, mononuclear cell; interstitial, unilateral, focal, minimal
KIDNEY : Basophilia; tubular, unilateral, focal, minimal
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LUNG : Metaplasia; alveolar, osseous, single, minimal
VAGINA : Metestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; JOINT, FEMOROTIBIAL, LEFT; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1506	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
THYMUS : Apoptosis, increased; minimal
VAGINA : Metestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1507	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

GLAND, ADRENAL : (Comment) left Damaged At Necropsy.
STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; multifocal, minimal
LUNG : Metaplasia; alveolar, osseous, single, minimal
THYMUS : Hemorrhage; minimal
VAGINA : Proestrus
NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1508	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

KIDNEY : Discoloration, pale; bilateral (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
LUNG : Inflammation, mixed cell; perivascular, multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
VAGINA : Estrus
NO CORRELATE : No correlating lesion [KIDNEY : Discoloration, pale; bilateral (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1509	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
NERVE, OPTIC : (Note) One Of A Pair Available For Evaluation.
STOMACH : Hemorrhage; focal, minimal, glandular
STOMACH : Erosion; focal, minimal, glandular [STOMACH : Focus, dark; multifocal, glandular (G)]
VAGINA : Metestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1510	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PITUITARY : (Note) Only Pars Distalis Available For Evaluation.
VAGINA : Metestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1511	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

BRAIN : (Comment) Damaged At Necropsy.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1512	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

KIDNEY : (Comment) Left Damaged At Necropsy.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1513	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1514	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	1515	Group:	1	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	0 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

NERVE, TIBIAL : (Comment) Right doubtful

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2001	Group:	2	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

SKIN : Scab; multifocal, muzzle (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [SKIN : Scab; multifocal, muzzle (G)]

Histopathology - The following Tissues were Within Normal Limits:

SKIN

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2002	Group:	2	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2003	Group:	2	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

GLAND, SEMINAL VESICLE : (Comment) Damaged At Necropsy.
STOMACH : Focus, dark; focal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; focal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

STOMACH

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2004	Group:	2	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

EYE : (Comment) right Damaged At Necropsy.
STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

STOMACH

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2005	Group:	2	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2006	Group:	2	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

STOMACH

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2007	Group:	2	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2008	Group:	2	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2009	Group:	2	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

LIVER : Hernia; left, right, medial lobe : (Comment) diaphragmatic
SKIN : Thin hair coat; focal, abdominal : (Comment) taken with mammary gland (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [SKIN : Thin hair coat; focal, abdominal : (Comment) taken with mammary gland (G)]

Histopathology - The following Tissues were Within Normal Limits:

SKIN

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2010	Group:	2	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; focal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; focal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

STOMACH

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2501	Group:	2	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

BRAIN : (Comment) Damaged At Necropsy.
STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

STOMACH : Hemorrhage; multifocal, minimal, glandular [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2502	Group:	2	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

GLAND, PITUITARY : (Comment) Damaged At Necropsy.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2503	Group:	2	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2504	Group:	2	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2505	Group:	2	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2506	Group:	2	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2507	Group:	2	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2508	Group:	2	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2509	Group:	2	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	2510	Group:	2	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	500 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3001	Group:	3	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

STOMACH

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3002	Group:	3	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3003	Group:	3	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3004	Group:	3	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

LARGE INTESTINE, RECTUM : (Comment) Damaged At Necropsy.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3005	Group:	3	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3006	Group:	3	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

STOMACH

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3007	Group:	3	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3008	Group:	3	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

STOMACH : Hemorrhage; focal, minimal, glandular [STOMACH : Focus, dark; multifocal, glandular (G)]
NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3009	Group:	3	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

STOMACH

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3010	Group:	3	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3501	Group:	3	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3502	Group:	3	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3503	Group:	3	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3504	Group:	3	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3505	Group:	3	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

GLAND, LACRIMAL : (Comment) Left organ doubtful

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3506	Group:	3	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3507	Group:	3	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

OVARY : (Comment) left Damaged At Necropsy.
SKIN : Thin hair coat; focal, thoracic,ventral (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [SKIN : Thin hair coat; focal, thoracic,ventral (G)]

Histopathology - The following Tissues were Within Normal Limits:

SKIN

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3508	Group:	3	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; focal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; focal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

STOMACH

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3509	Group:	3	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

GLAND, PITUITARY : (Comment) Damaged At Necropsy.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	3510	Group:	3	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	1000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4001	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

BRAIN : (Comment) Damaged At Necropsy.
EPIDIDYMIS, LEFT : Small (TGL)
TESTIS, LEFT : Small
TESTIS, LEFT : Abnormal appearance; soft
TESTIS, RIGHT : Enlargement (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

EPIDIDYMIS, LEFT : Depletion; marked, sperm [EPIDIDYMIS, LEFT : Small (G)]
GLAND, HARDERIAN : Infiltration, mononuclear cell; multifocal, minimal
HEART : Infiltration, mononuclear cell; myocardial, focal, minimal
LIVER : Infiltration, mononuclear cell; multifocal, minimal
PANCREAS : Atrophy; acinar, focal, minimal
NO CORRELATE : No correlating lesion [TESTIS, RIGHT : Enlargement (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4002	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR, LEFT : Enlargement (TGL)
LYMPH NODE, MANDIBULAR, RIGHT : Enlargement (TGL)
SKIN : Thin hair coat; focal, abdominal (TGL)
STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, follicle [LYMPH NODE, MANDIBULAR, LEFT : Enlargement (G)]
LYMPH NODE, MANDIBULAR, RIGHT : Cellularity, increased; alveolar, minimal, follicle [LYMPH NODE, MANDIBULAR, RIGHT : Enlargement (G)]
NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G) | SKIN : Thin hair coat; focal, abdominal (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4003	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

GLAND, PROSTATE : (Comment) Damaged At Necropsy.
LIVER : Hernia; right, medial lobe : (Comment) Diaphragmatic
LIVER : Focus, dark; right, focal, medial lobe (TGL)
SKIN : Thin hair coat; focal, abdominal : (Comment) Taken with mammary gland (TGL)
STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LIVER : Necrosis; hepatocellular, focal, mild [LIVER : Focus, dark; right, focal, medial lobe (G)]
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LIVER : Fibrosis; capsular, focal, minimal
NO CORRELATE : No correlating lesion [SKIN : Thin hair coat; focal, abdominal : (Comment) Taken with mammary gland (G) | STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4004	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; focal, glandular (TGL)
URINARY BLADDER : (Comment) Damaged At Necropsy.poorly infused

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
THYMUS : Apoptosis, increased; minimal
NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; focal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4005	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4006	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

GLAND, PROSTATE : (Comment) Damaged At Necropsy.
KIDNEY : Discoloration, pale; bilateral (TGL)
LARGE INTESTINE, RECTUM : (Comment) Damaged At Necropsy.
STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
STOMACH : Edema; submucosal, minimal, glandular
THYMUS : Hemorrhage; mild
NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G) | KIDNEY : Discoloration, pale; bilateral (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; TESTIS, RIGHT; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4007	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR, LEFT : Enlargement (TGL)
LYMPH NODE, MANDIBULAR, RIGHT : Enlargement (TGL)
STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; mild, follicle [LYMPH NODE, MANDIBULAR, LEFT : Enlargement (G)]
LYMPH NODE, MANDIBULAR, RIGHT : Cellularity, increased; mild, follicle [LYMPH NODE, MANDIBULAR, RIGHT : Enlargement (G)]
STOMACH : Hemorrhage; multifocal, minimal, glandular [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; TESTIS, RIGHT; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4008	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

KIDNEY : Basophilia; tubular, unilateral, focal, minimal
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
THYMUS : Hemorrhage; mild
NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4009	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PITUITARY : (Note) Only Pars Distalis Available For Evaluation.
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
NERVE, OPTIC : (Note) One Of A Pair Available For Evaluation.
PANCREAS : Atrophy; acinar, focal, minimal
STOMACH : Erosion; focal, minimal, glandular
THYMUS : Apoptosis, increased; minimal
NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; multifocal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; TESTIS, RIGHT; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4010	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
THYMUS : Hemorrhage; minimal

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; EPIDIDYMIS, LEFT; EPIDIDYMIS, RIGHT; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, COAGULATING; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TESTIS, RIGHT; TONGUE; TRACHEA; URINARY BLADDER

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4011	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4012	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; focal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; focal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

STOMACH

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4013	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4014	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4015	Group:	4	Sex:	Male
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4501	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

KIDNEY : Discoloration, pale; bilateral (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
VAGINA : Proestrus
NO CORRELATE : No correlating lesion [KIDNEY : Discoloration, pale; bilateral (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4502	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, follicle
VAGINA : Diestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4503	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

VAGINA : Diestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4504	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; multifocal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

STOMACH : Hemorrhage; focal, minimal, glandular [STOMACH : Focus, dark; multifocal, glandular (G)]
VAGINA : Metestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4505	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	91 (13)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

STOMACH : Focus, dark; focal, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, follicle
VAGINA : Diestrus
NO CORRELATE : No correlating lesion [STOMACH : Focus, dark; focal, glandular (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4506	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

UTERUS : Abnormal content

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PITUITARY : (Note) Only Pars Distalis Available For Evaluation.
LIVER : Infiltration, mononuclear cell; multifocal, minimal
VAGINA : Proestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4507	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

VAGINA : Estrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MANDIBULAR, LEFT; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4508	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

KIDNEY : Discoloration, pale; bilateral (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PARATHYROID : (Note) One Of A Pair Available For Evaluation.
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
VAGINA : Metestrus
NO CORRELATE : No correlating lesion [KIDNEY : Discoloration, pale; bilateral (G)]

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4509	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

KIDNEY : Infiltration, mononuclear cell; unilateral, focal, minimal
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
NERVE, OPTIC : (Note) One Of A Pair Available For Evaluation.
PANCREAS : Infiltration, mononuclear cell; interstitial, multifocal, minimal
THYMUS : Hemorrhage; minimal
VAGINA : Estrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4510	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Terminal Euthanasia		
		Study Day (Week) of Death:	92 (14)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

GLAND, PITUITARY : (Note) Only Pars Distalis Available For Evaluation.
LYMPH NODE, MANDIBULAR, LEFT : Cellularity, increased; minimal, plasma cell
VAGINA : Diestrus

Histopathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW, STERNUM; BONE, FEMUR; BONE, STERNUM; BRAIN; BRAIN, OLFACTORY BULB; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; JOINT, FEMOROTIBIAL, LEFT; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histopathology - The following Tissues were Not Examined:

None

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Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4511	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

Appendix 27
Appendix 2

30-Mar-2023 10:33:52

Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4512	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

Appendix 27
Appendix 2

30-Mar-2023 10:33:52

Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4513	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

Appendix 27
Appendix 2

30-Mar-2023 10:33:52

Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4514	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

Appendix 27
Appendix 2

30-Mar-2023 10:33:52

Individual Macroscopic and Microscopic Pathology

(b) (4)

Animal:	4515	Group:	4	Sex:	Female
Species:	Rat	Strain:	Han Wistar		
		Dose:	2000 mg/kg /day		
		Removal Reason:	Recovery Euthanasia		
		Study Day (Week) of Death:	120 (18)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Animal Details:

No animal details found

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 27

SIGNATURE(S) FOR DOCUMENT: (b) (4) - (b) (4) **Pathology Final Report**

Individual Scientist:	I approve this document.	
Name:	(b)(6)	
Electronically Signed in (b) (4)		01-Aug-2023 09:21:40 (UTC+00:00) Timestamp

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 28

PATHOLOGY PEER REVIEW CERTIFICATE

Study number:
(b) (4)

Study Title:
90-Day Repeated Dose Toxicity Study of TRP Pro by the Oral (gavage) Route in the Wistar Han IGS Rat With a 4-Week Recovery Period

PURPOSE: The purpose of this pathology peer review was to assess the overall quality and consistency of the microscopic data and determine the validity of the study pathologist's conclusions.
A pathology peer review for this study was performed as follows for this study:

MATERIALS AND METHODS:

1. Review of protocol and amendments, pathology report, histology records, clinical observations, organ weight data, clinical pathology data, etc.
2. Review of all tissues from the Male and Female Group 4, animal numbers: 4001, 4002, 4009, 4010, 4501, 4502, 4509 and 4510.

RESULTS:

Any differences of opinion were resolved and agreement on terminology and diagnoses was achieved. The histopathology tables and corresponding narrative in the pathology report reflect the diagnoses and conclusions agreed to by the peer review pathologist.

All electronic signatures appear at the end of the document.

(b)(6)

Sponsor Reference No. (b) (4) Test Facility Study No. (b) (4)

Appendix 28

SIGNATURE(S) FOR DOCUMENT: (b) (4) - (b) (4) Pathology Final Report Peer Review Certificate

Approval Signature: I approve this document.

Name: (b)(6)

01-Aug-2023 10:01:57 (UTC+00:00)

Electronically Signed in (b) (4) Timestamp

SIGNATURE(S) FOR DOCUMENT: (b) (4) **General Toxicology Final Report**

QA Approval: I approve the Quality Assurance Statement for this report.

Name: (b) (4), (b)(6), (b) (3) (B)

24-Oct-2023 08:46:06 (UTC+00:00)

Electronically Signed in (b) (4) Timestamp

Study Director Approval: I approve this Report.

Name: (b)(6)

24-Oct-2023 09:47:31 (UTC+00:00)

Electronically Signed in (b) (4) Timestamp

(b) (4)

FINAL REPORT

Test Facility Study Code: (b) (4)

A GLP Bacterial Reverse Mutation Assay of L-tryptophan (TRP Pro)

SPONSOR:
CJ CheilJedang Corporation
55-42 Beongil Gwanggyo-ro,
Yeongtong-gu Suwon-si,
16495 Gyeonggi-do,
Republic of Korea

(b) (4)

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STATEMENT OF THE STUDY DIRECTOR

This study has been performed in accordance with the Study Plan and its amendment agreed upon by the Sponsor, the OECD Guidelines for Testing of Chemicals (No. 471, 2020), Commission Regulation (EC) No.440/2008, B.13/14., EPA Health Effects Test Guidelines, OPPTS 870.5100 (EPA 712-C-98-247, 1998) and the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17).

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in this study. By virtue of my dated signature I accept the responsibility for the validity of the data.

No chemical analysis of the dose formulation was performed as part of this study. Traceability (equipment used, quantities of test item weighed etc.) of dosing formulation preparations was checked and revealed no abnormalities of consequences. Furthermore, for this study, the formulations were prepared just before the treatment. Consequently, the absence of dose formulation analysis data was considered not to prejudice the overall GLP status of the study and the scientific reliability of the study conclusions.

Signature: (b)(6)

Date: 19 September 2022

STATEMENT OF THE MANAGEMENT

According to the conditions of the research and development agreement between CJ CheilJedang Corporation (as Sponsor) and (b) (4) (as Test Facility), the study titled "A GLP Bacterial Reverse Mutation Assay of L-tryptophan (TRP Pro)" has been performed in compliance with the Study Plan and the Principles of Good Laboratory Practice.

Signature: (b)(6)

Date: 19 September 2022

QUALITY ASSURANCE STATEMENT

Study Code: 21/300-007M

Study Title: A GLP Bacterial Reverse Mutation Assay of L-tryptophan (TRP Pro)

This Study has been audited by (b) (4) in accordance with the applicable Good Laboratory Practice regulations. Audit reports were submitted in accordance with SOPs as follows:

Date of inspection	Phase(s) Inspected/Audited	Date of report to	
		Management	Study Director
11 December 2021	Study Plan	22 February 2022	22 February 2022
25 January 2022	Amendment 1 to the Study Plan	22 February 2022	22 February 2022
23 February 2022	Amendment 2 to the Study Plan	29 March 2022	29 March 2022
26 January 2022	Formulation	22 February 2022	22 February 2022
06 January 2022	Treatment	06 January 2022	06 January 2022
10 January 2022	Observation	10 January 2022	10 January 2022
26 March 2022	Draft Report	19 April 2022	19 April 2022
16 September 2022	Final Report	16 September 2022	16 September 2022

In addition to the above-mentioned audits, (which may include study specific inspections and/or relevant process based inspections) routine facility inspections were also conducted.

The Final Report reflects the raw data and accurately and completely describes the methods and procedures of the study.

Signature: (b)(6) Date: 19. September 2022

1. SUMMARY

The test item L-tryptophan (TRP Pro) was tested for potential mutagenic activity using the Bacterial Reverse Mutation Assay.

The experiments were carried out using histidine-requiring auxotroph strains of *Salmonella typhimurium* (*Salmonella typhimurium* (b) (4)) in the presence and absence of a post mitochondrial supernatant (S9 fraction) prepared from the livers of phenobarbital/β-naphthoflavone-induced rats.

The study included a Preliminary Compatibility Test, a Preliminary Concentration Range Finding Test (Plate Incorporation Method), an Assay 3 (Plate Incorporation Method) and an Assay 4 (Pre-Incubation Method).

Based on the results of the Compatibility Test, the test item (b) (4)

Note: 16 test item containers were received from the Sponsor (container 1 was used for Genotoxicity studies in Assays 3 and 4; container 4 was used in the Preliminary Range Finding Test, Assay 1 and Assay 2). In Assay 2 the supplied test item resulted in plate infection at higher concentrations with pre-incubation (indicating bacterial or fungal contamination of the test item). The colony counting could be performed in the presence of the infection.

Additional confirmatory experiments were performed to clarify the results on the observed infections (due to the test item used from container 4) in Assay 2. In Assay 2 excessive infection was observed in S*almonella typhimurium* (b) (4) strains with and without metabolic activation at higher concentrations. In these cases, the higher concentration of analyzable doses did not meet the recommendations of the test guidelines. Results of Assay 1 and Assay 2 are considered as invalid experiments and is not reported; however, all data are kept and archived in the raw data binder.

Precipitate/ slight precipitate was detected on the plates in the main tests in all examined bacterial strains with and without metabolic activation at higher concentrations.

Inhibitory, cytotoxic effect of the test item (reduced/ slight reduced background lawn development) was observed in the main tests in all examined bacterial strains with and without metabolic activation at higher concentrations.

In the assays the number of revertant colonies did not show any biologically relevant increase compared to the solvent controls. There were no reproducible dose-related trends and there was no indication of any treatment-related effect.

The mean values of revertant colonies of the negative (vehicle/solvent) control plates were within the historical control range, the reference mutagens showed the expected increase in the number of revertant colonies, the viability of the bacterial cells was checked by a plating experiment in each test. At least five analyzable concentrations were presented in all strains of the main tests, the examined concentration range was considered to be adequate. The study was considered to be valid.

Note: Salmonella typhimurium TA102 of bacterial strain data of the untreated and DMSO controls in the Assay 4 were slightly lower than the bottom limit of the historical control range.

This fact has no impact on the results or integrity of the study since the control materials showed clear negative effects.

The reported data of this mutagenicity assay show that under the experimental conditions applied the test item **did not induce gene mutations by base pair changes or frameshifts or cross-linking in the genome of the strains used.**

In conclusion, the test item L-tryptophan (TRP Pro) (Batch number: (b) (4)) had no mutagenic activity on the growth of the bacterial strains under the test conditions used in this study.

2. OBJECTIVE

The purpose of this study was to evaluate the mutagenic potential of the test item by measuring its ability to induce reverse mutations at selected loci of several strains of *Salmonella typhimurium* in the presence and absence of activated rat liver S9 fraction.

The bacterial reverse mutation test is a microbial assay which detects point mutations induced by chemicals causing base changes or frameshift mutations in the genome of amino-acid requiring strains of *Salmonella typhimurium*. The auxotrophic *S. typhimurium* strains are unable to grow on minimal medium - containing inorganic salts and glucose as a carbon source - except for spontaneous revertants. But in the presence of a mutagenic agent, some of them can be converted to prototrophs after a reverse mutation to the wild type. These revertants can grow and form colonies in minimal medium. An increased number of the revertant colonies indicates mutagenic activity of the test item.

The *Salmonella typhimurium* histidine (his) reversion system measures $his^- \rightarrow his^+$ reversions. The *Salmonella typhimurium* strains are constructed to differentiate between base-pair (b) (4), frameshift (b) (4) and cross-linking (b) (4) mutations.

The bacteria used in this assay did not possess the mammalian enzyme system that is known to convert promutagens into mutagenic metabolites. In order to overcome this major drawback, an exogenous metabolic activation system is added in the form of a mammalian microsomal enzyme activation mixture (liver extract, S9 fraction). The activation system uses nicotinamide-adenine dinucleotide phosphate (NADP+)-cytochrome P450 dependent mixed function oxidase enzymes of the liver. The liver extract was obtained from rats, which were pre-treated with phenobarbital and β-naphthoflavone, two inducers of several drug-metabolizing enzymes.

The bacterial mutagenicity test, along with other short-term assays, is used extensively to evaluate substances for mutagenic activity. Some mutagens (e.g.: nitrosamines) are poorly detected in the standard plate incorporation assay, but they can be detected by the pre-incubation assay; both approaches are considered to assess the mutagenicity of the test item.

3. STUDY SCHEDULE

Date of Study Plan:	11 January 2022
Date of Amendment 1 to the Study Plan:	25 January 2022
Date of Amendment 2 to the Study Plan:	22 February 2022
Experimental Starting Date:	11 January 2022
Range Finding Test:	11–13 January 2022
Assay 1:	26–28 January 2022
Assay 2:	01–03 February 2022
Assay 3:	23–25 February 2022
Assay 4:	01–03 March 2022
Experimental Completion Date:	03 March 2022
Draft Report:	26 March 2022
Final Report:	19 September 2022

4. SPONSOR

(b) (4), (b)(6)

6. JUSTIFICATIONS AND GUIDELINES

6.1. Justification of Test System and Number of Replicates

Salmonella typhimurium ((b) (4)) bacterial strains were selected to be used in the study as these are the preferred bacterial strains for AMES Test based on the OECD No. 471 guideline, and it was also used in the method validation study of the Test Facility.

Three replicates were used in the study which is the minimum requirement of the OECD 471.

6.2. Guidelines for Study

This study was following the procedures indicated by the following internationally accepted guidelines and recommendations:

- Ninth Addendum to OECD Guidelines for Testing of Chemicals, Section 4, No. 471, "Bacterial Reverse Mutation Test", Adopted 1997, Corrected 2020
- EPA Health Effects Test Guidelines, OPPTS 870.5100 "Bacterial Reverse Mutation Test", EPA 712-C-98-247, 1998
- Commission Regulation (EC) No. 440/2008, B.13/14. "Mutagenicity: Reverse Mutation Test Using Bacteria", 2008

7. TEST MATERIALS

7.1. Test Item Characterization

The test item of a suitable chemical purity was provided by the Sponsor. All precautions required in the handling and disposal of the test item were outlined by the Sponsor. The test item was identified on the basis of the information supplied by the Sponsor in the Pharmacy at (b) (4) Copy of the Certificate of Analysis is shown in Appendix 1.

7.2. Test Item Identification

Information provided by the Sponsor:

Name: L-tryptophan (TRP Pro)

CAS number: 73-22-3

Batch/Lot number: (b) (4)

Description: Light brown granule

Purity: 61.34%

Manufacturer/supplier: CJ CheilJedang

Manufacturing date: 05 October 2021

Expiry date: 04 October 2023

*Note: 16 test item containers were received from the Sponsor (container 1 was used for Genotoxicity studies in Assays 3 and 4; container 4 was used in Preliminary Range Finding Test and Assays 1 and 2).

As agreed with the Sponsor, no correction for purity of the test item was applied, to the test item as it is considered as a pure substance.

7.3. Stability of Bulk Test Item

The test item is considered stable when stored under appropriate storage conditions: Controlled room temperature (15–25 °C, ≤ 70% relative humidity), protected from light and humidity (tightly closed container). The test item is stored in the Pharmacy of the Test Facility.

7.4. Control Items Identification

Positive, negative (solvent) and untreated controls were included in the experiments. Routine safety precautions (lab coat, gloves, safety glasses and face mask) were applied to assure personnel health and safety.

Note: Untreated, negative and positive controls used Assay 3 (*S. typhimurium* TA98 and TA100) was part of a concurrent study (study code: 21/280-007M)

7.5. Positive Control Items Identification

Strain specific positive controls were included in the assay, which demonstrated the effective performance of the test. The strain specific positive control chemicals are summarized in Text Table 1.

Text Table 1: Strain-Specific Positive Control Chemicals

Metabolic activation	Strain specific positive chemical		Vehicle	Dose quantity/plate	Strain
	Chemical and Supplier	Batch number / Expiry date			
non-activation	4-nitro-1,2-phenylene-diamine (NPD) (b) (4)	(b) (4)	DMSO	4 µg	*S. typhimurium* (b) (4)
non-activation	Sodium azide (SAZ) (b) (4)		Distilled water	2 µg	*S. typhimurium* (b) (4)
non-activation	9-aminoacridine (9AA) (b) (4)		DMSO	50 µg	*S. typhimurium* (b) (4)
non-activation	Mitomycin C (MC) (b) (4)		Distilled water	2.5 µg	*S. typhimurium* (b) (4)
activation	2-aminoanthracene (2AA) (b) (4)		DMSO	2 µg	all *Salmonella* strains
activation	2-aminoanthracene (2AA) (b) (4)		DMSO	10 µg	*S. typhimurium* (b) (4)

Abbreviation for tester strains: *S. typhimurium*: *Salmonella typhimurium*

7.6. Negative Control Items Identification (Solvent Control)

In the study two vehicle (solvent) control groups were used depending on the solubility of the test item and the solubility of strain specific positive control chemicals. The following chemicals were used for vehicle (solvent) control groups:

Dimethyl sulfoxide (DMSO):

(b) (4)

7.7. Reserve Sample

For each batch (lot) of the test item and positive control items, a reserve sample (as specified in the relevant SOP) was collected and maintained under the appropriate storage conditions in the Archives of the Test Facility.

7.8. Test Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of test materials (including empty containers of Sponsor-provided materials) was maintained. All unused Sponsor-supplied bulk test materials, with the exception of reserve samples, will be returned to the Sponsor after the finalization of the study report.

Note: Based on the sponsor's request the test item will be returned instead of disposed.

7.9. Safety

All precautions required in the handling and disposal of the test item were outlined by the Sponsor. Routine safety precautions (gloves, goggles, face mask, lab coat) for unknown materials will be applied to ensure personnel health and safety.

8. ADDITIONAL MATERIALS

The chemicals used in the independently performed experiments of the study are summarized in Text Table 2.

Text Table 2: Chemicals Used in the Experiments

Chemical	Manufacturer / Supplier	Batch Number	Expiry date
Acetone	(b) (4)		25 March 2024
Agar Bacteriological			30 September 2023
D-Biotin			31 January 2024
Distilled water			29 March 2022
Distilled water			25 May 2022
D-Glucose 6-phosphate Na			31 October 2023

Chemical	Manufacturer / Supplier	Batch Number	Expiry date
L-Histidine HCl x H_2O	(b) (4)		30 April 2024
KCl			26 March 2024
$MgCl_2$ x 6 H_2O			31 December 2023
N, N-Dimethylformamide (DMF)			25 February 2025
NADP Na			01 February 2022
NADP Na			07 November 2022
NaCl			17 April 2025
NaH_2PO_4 x H_2O			31 March 2026
Na_2HPO_4 x $12H_2O$			31 March 2022
Nutrient Agar			01 April 2025
Nutrient Broth No.2			31 July 2025
Nutrient Broth No.2			31 March 2026

NADP: β-Nicotinamide adenine dinucleotide phosphate

9. DOSE FORMULATION AND ANALYSIS

9.1. Preparation of Formulations

Distilled water was used as solvent to prepare the stock solution of the test material (based on the available information and the performed trial formulation). Test solutions were freshly prepared at the beginning of the experiments in the testing laboratory by diluting the stock solution using the selected solvent. The stock solution was in ultrasonic water bath for 12-minutes.

As agreed with the Sponsor, no correction for purity of the test item was applied.

Text Table 3: Formulation of the Test Item for the Main Experiments

No. of concentration	Concentration of the test item	Concentration (µg test item/plate)
1	(b) (4)	5000
2		1581
3		500
4		158.1
5		50
6		15.81
7		5
8		1.581

Concentrations 1–7 were examined in the Assay 1 and Assay 3 (Initial Mutation Test using the plate incorporation method) and concentrations 1–8 were examined in the Assay 2 and Assay 4 (Confirmatory Mutation Test using the pre-incubation method).

9.2. Sample Collection and Analysis

Analytical determination of the test item concentration, stability and homogeneity was not performed because of the character and the short period of study.

10. TEST SYSTEM

10.1. Bacterial Strains

10.1.1. Origin

Date of arrival and origin:

Salmonella typhimurium (b) (4) 17 February 2021, (b) (4)

Salmonella typhimurium (b) (4) 17 February 2021, (b) (4)

Salmonella typhimurium (b) (4) 17 February 2021, (b) (4)

Salmonella typhimurium (b) (4) 17 February 2021, (b) (4)

Salmonella typhimurium (b) (4) 10 January 2018, (b) (4)

The true copies of original certificates and other documents of the strains are collected and stored in the Microbiological Laboratory of (b) (4).

10.1.2. Genotypes

In addition to histidine mutation, each strain has additional mutations, which enhances its sensitivity to mutagens. The *uvrB* (*uvrA*) strains are defective in excision repair, making them more sensitive to the mutagenic and lethal effects of a wide variety of mutagens because they cannot repair DNA damages. The presence of *rfa* mutation increases the permeability of the bacterial lipopolysaccharide wall for larger molecules. The plasmid pKM101 (TA98, TA100, TA102) carries the *muc*+ gene which participates in the error-prone "SOS" DNA repair pathway induced by DNA damage. This plasmid also carries an ampicillin resistance transfer factor (R-factor) which is used to identify its presence in the cell. The genotypes of the tester strains used for mutagenicity testing are summarized in Text Table 4.

Text Table 4: Genotypes of the Strains Used for Mutagenicity Testing

Strain	Genotype		Mutations		Main DNA target	Plasmid
	trp./his mutation	type of mutation	cell wall	DNA- repair		
S. typhimurium (b) (4)	*hisD3052*	Frameshift	*rfa*	*uvrB*	GC	pKM101
S. typhimurium (b) (4)	*hisG46*	Base pair substitution	*rfa*	*uvrB*	GC	pKM101
S. typhimurium (b) (4)	*hisG46*	Base pair substitution	*rfa*	*uvrB*	GC	No
S. typhimurium (b) (4)	*hisC3076*	Frameshift	*rfa*	*uvrB*	GC	No
S. typhimurium (b) (4)	*hisG428*	Base pair substitution, Cross-linking	*rfa*	*uvrB*	AT	pKM101, pAQ1

Abbreviations of tester strains: *S. typhimurium: Salmonella typhimurium*

10.1.3. Storage

The strains are stored at -80 ± 10 °C in the Culture Collection of the Microbiological Laboratory of (b) (4) Frozen permanent cultures of the tester strains were prepared from fresh, overnight cultures to which DMSO was added as a cryoprotective agent.

10.1.4. Confirmation of phenotypes of tester strains

The phenotypes of the tester strains used in the bacterial reverse mutation assays with regard to membrane permeability (*rfa*), UV sensitivity (*uvrB*), ampicillin resistance (*amp*), as well as spontaneous mutation frequencies are checked regularly according to Ames et al. [1] and Maron and Ames [2].

Established procedures (Standard Operating Procedures) for the preparations of each batch of frozen stock culture, raw data and reports of phenotype confirmation are stored in the Microbiological Laboratory of (b) (4).

10.1.5. Spontaneous reversion of tester strains

Each test strain reverts spontaneously at a frequency that is characteristic of the strain. Spontaneous reversion of the test strains to histidine (*Salmonella typhimurium* strains) independence is measured routinely in mutagenicity experiments and expressed as the number of spontaneous revertants per plate.

Historical control values for spontaneous revertants (revertants/plate) for untreated control sample without and with metabolic activation in the period of 2015–2020 were (as guide) as follows: *Salmonella typhimurium* (b) (4) 11–50, 13–54, (b) (4): 67–152, 67–152, TA1535: 1–33, 3–39, (b) (4): 2–26, 1–29, *Salmonella typhimurium* (b) (4) (2019): 264–326, 264–392. More detailed historical control data are shown in Appendix 2.

10.1.6. Procedure for growing cultures

The frozen bacterial cultures were thawed at room temperature and 200 µL inoculum were used to inoculate each 50 mL of Nutrient Broth No.2 (Section 10.2.2.) for the overnight cultures in the assay. The cultures were incubated for 10–14 hours at 37 °C in a gyrotory water bath shaker.

10.1.7. Viability of the testing cultures

The viability of each testing culture was determined by plating 0.1 mL of the 10^5, 10^6, 10^7 and 10^8 dilutions prepared by sterile physiological saline on Nutrient Agar (Section 10.2.3.) plates. The viable cell number of the cultures was determined by manual counting after approximately 24-hour incubation at (b) (4) °C.

10.2. Media

The supplier, batch number and expiry date of the used chemicals described in sections 10.2.2.-10.2.4. are summarized in Text Table 2 (Chemicals used in the experiments table in Section 8.). The composition of media refers to 1000 mL.

10.2.1. The typical composition (g/1000 mL) of minimal glucose agar

Glucose	20.0	g
Magnesium sulfate	0.2	g
Citric acid	2.0	g
di-Potassium hydrogenphosphate	10.0	g
Sodium ammonium hydrogenphosphate	3.5	g
Agar agar	13.0	g
Distilled water	q.s. ad[1] 1000	mL

Minimal glucose agar plates (Batch number: (b) (4) Expiry date: 08 March 2022 was used in Preliminary Range Finding Test; Batch number: (b) (4) Expiry date: 31 May 2022 was used in Assay 3; Batch number: (b) (4) Expiry date: 07 June 2022 was used in Assay 4) were provided by (b) (4) Certificate of Analysis were obtained from the Supplier.

10.2.2. Nutrient broth No.2

Nutrient Broth No.2	25.0	g
Distilled water	q.s. ad 1000	mL

[1] q.s. ad = quantum sufficiat ad (a sufficient quantity to make)

Sterilization was performed at (b) (4).

10.2.3. Nutrient agar

Nutrient Agar	20.0	g
Distilled water	q.s. ad 1000	mL

Sterilization was performed at (b) (4).

10.2.4. Top agar for *Salmonella typhimurium* strains

Agar solution:

Agar bacteriological	4.0	g
NaCl	5.0	g
Distilled water	q.s. ad 1000	mL

Sterilization was performed at (b) (4).

Histidine – Biotin solution (0.5 mM):

D-Biotin (F.W. 244.31)	122.2	mg
L-Histidine x·HCl x H_2O (F.W. 209.63)	104.8	mg
Distilled water	q.s. ad 1000	mL

Sterilization was performed by (b) (4).

Complete Top agar for *Salmonella typhimurium* strains:

Histidine – Biotin solution (0.5 mM)	100	mL
Agar solution	900	mL

10.3. Metabolic Activation System

Test bacteria were also exposed to the test item in the presence of an appropriate metabolic activation system, which is a cofactor-supplemented post-mitochondrial S9 fraction.

The post-mitochondrial fraction (S9 fraction) was prepared by the Microbiological Laboratory of (b) (4). according to Ames et al. [1] and Maron and Ames [2]. The documentation of the preparation of this post-mitochondrial fraction is stored in the reagent notebook in the Microbiological Laboratory which is archived yearly.

The supplier, batch number and expiry date of the used chemicals described in sections 10.3.3. and 10.3.4. are summarized in Text Table 2 (Chemicals used in the experiments table in Section 8.). The composition of solution refers to 1000 mL.

10.3.1. Induction of liver enzymes

Male Wistar rats (502–719 g, animals were 26–29 weeks old and 290–330 g, animals were 9–10 weeks old) were treated with phenobarbital (PB) and β-naphthoflavone (BNF) at 80 mg/kg bw/day by oral gavage for three consecutive days. Rats were given drinking water and food *ad libitum* until 12 h before sacrifice when food was removed. Sacrifice was by ascending concentration of CO_2, confirmed by cutting through major thoracic blood vessels. Initiation of the induction of liver enzymes used for preparation S9 used in this study were 28 June 2021 and 27 September 2021.

10.3.2. Preparation of rat liver homogenate S9 fraction

On Day 4, the rats were euthanized and the livers were removed aseptically using sterile surgical tools. After excision, livers were weighed and washed several times in 0.15 M KCl. The washed livers were transferred to a beaker containing 3 mL of 0.15 M KCl per g of wet liver, and homogenized. Homogenates were centrifuged for 10 min at 9000 g and the supernatant was decanted and retained. The freshly prepared S9 fraction was aliquoted into 1–5 mL portions, frozen quickly and stored at -80 ± 10 °C. The date of preparation of S9 fractions for this study was 01 July 2021 and 30 September 2021 ((b) (4), Expiry date: 01 July 2023 and (b) (4) Expiry date: 30 September 2023).

*Note: This batch was used in Assay 3 and Assay 4.

The sterility of the preparation was confirmed in each case. The protein concentration of the preparation was determined by a chemical analyzer at 540 nm in the Clinical Chemistry Laboratory of (b) (4) . The mean protein concentration of the S9 fraction used were determined to be 25.1 g/L and 24.4 g/L.

The biological activity in the *Salmonella* assay of S9 was characterized in each case using the two mutagens 2-Aminoanthracene and Benzo(a)pyrene, that requires metabolic activation by microsomal enzymes. The batches of S9 used in this study functioned appropriately.

10.3.3. The S9 Mix (containing 10% (v/v) of S9)

Salt solution for S9 Mix:

NADP Na	7.66 g
D-glucose-6 phosphate Na	3.53 g
$MgCl_2$ x 6 H_2O	4.07 g
KCl	6.15 g
Distilled water	q.s. ad 1000 mL

Sterilization was performed by filtration through a 0.22 µm membrane filter.

The complete S9 mix was freshly prepared containing components as follows:

Ice cold 0.2 M sodium phosphate buffer, pH 7.4	500 mL
Rat liver homogenate (S9)	100 mL
Salt solution for S9 Mix (see above)	400 mL

Prior to addition to the culture medium the S9 mix was kept in an ice bath.

10.3.4. 0.2 M Sodium phosphate buffer, pH 7.4

Solution A:

Na_2HPO_4 x 12 H_2O	71.63 g
Distilled water	q.s. ad 1000 mL

Sterilization was performed at 121 °C in an autoclave.

Solution B:

NaH_2PO_4 x H_2O	27.6 g
Distilled water	q.s. ad 1000 mL

Sterilization was performed at 121 °C in an autoclave.

0.2M Sodium phosphate buffer pH 7.4:

Solution A	880 mL
Solution B	120 mL

11. TEST PROCEDURE

The study included a Preliminary Compatibility Test, a Preliminary Range Finding Test, and main tests. In the Preliminary Range Finding Test and Assay 3, the plate incorporation method, in the Assay 4 the pre-incubation method was used.

Of the 16 containers supplied for the project, containers numbered 2-16 had no special information on the label, container 1 was marked to be used for genotoxicity assays (with same batch number and identical supplied information as the other containers). Container 4 was used for the Preliminary Compatibility Test and Preliminary Range Finding Test, and also for Assay 1 and Assay 2. However, due to bacterial or fungal contamination of the test item (seen as growth of colonies on all higher concentration agar plates in the S*almonella typhimurium* pre-incubation assay phase), Assay 1 and Assay 2 were considered to be invalid. Data from the invalid parts of the study are archived but not

reported. Container 1 was used in Assays 3 and 4 (with no microbiological contamination) which were valid and are reported.

11.1. Concentrations

Concentrations for the main tests were selected on the basis of the Preliminary Compatibility Test and Preliminary Range Finding Test. In the main tests, different concentrations were used.

11.2. Preliminary Compatibility Test

The solubility of the test item was examined using distilled water, Dimethyl sulfoxide (DMSO), *N,N*-Dimethylformamide (DMF) and Acetone. The test item was partially soluble at 100 mg/mL concentration using distilled water. However at the same concentration insolubility was noted using DMSO, DMF and Acetone. The formulation at 50 mg/mL concentration using distilled water as vehicle was rapidly settling homogenous suspension approximately after 5-minutes ultrasonic water bath. Distilled water was selected as vehicle for the study. The obtained stock formulation (100 µL) with the solution of top agar (section 10.2.4.) and phosphate buffer (section 10.3.4.) was examined in a test tube without test bacterium suspension. The results of the Preliminary Compatibility Test are summarized in Text Table 5.

Text Table 5: The Solubility of the Test Item in distilled water

Concentration of test item in distilled water (mg/mL)	**Solubility in distilled water**	**Solubility in the top solution (test item formulation 100 µL + phosphate buffer 500 µL + top agar 2 mL)**	**Test item concentration in the test plate (µg/tube)**
50	sand-coloured suspension	opalescent	5000
25	sand-coloured suspension	slightly opalescent	2500
10	sand-coloured suspension	clear solution	1000

*Note: The sand colour was fading in a concentration related manner.

11.3. Preliminary Range Finding Test

Based on the solubility test, a 50 mg/mL stock solution was prepared in distilled water. Six test concentrations were prepared by successive dilutions of the stock solution, spaced by factors of 2, 2.5 and 4 times approximately √10. The revertant colony numbers and the inhibition of the background lawn of auxotrophic cells of two of the tester strains (*Salmonella typhimurium* (b) (4) and (b) (4)) were determined at concentrations of (b) (4) and (b) (4) µg/plate of the test item, in the absence and presence of metabolic activation. In the Preliminary Range Finding Test the plate incorporation method (section 11.7.) was used.

11.4. Test Item Concentrations in the Mutagenicity Tests (Assay 3 and Assay 4)

Based on the results of the preliminary test, a 50 mg/mL stock solution was prepared in distilled water, which was diluted by serial dilutions in several steps to obtain the dosing formulations for lower doses. The maximum test concentration was (b) (4) µg of test item/plate.

Examined concentrations in Assay 3 were (b) (4) and (b) µg/plate.

Examined concentrations in Assay 4 were (b) (4) and (b) (4) µg/plate.

11.5. Control Groups Used in the Tests

Strain-specific positive and negative (solvent) controls, both with and without metabolic activation were included in Assay 3 and Assay 4. In addition, an untreated control was used demonstrating that the

chosen vehicle induced no deleterious or mutagenic effects. The control groups used in the tests are listed in Text Table 6.

Text Table 6: Summary of Controls

Type of control	Activation with S9 Mix	Solvent	Top Agar	Strain-Specific Positive Chemical Solutions (section 7.5.)	Phosphate Buffer
Untreated	–	–	+	–	+
Untreated	+	–	+	–	–
Solvent	–	+	+	–	+
Solvent	+	+	+	–	–
Positive Reference Control	–	–	+	+	+
Positive Reference Control	+	–	+	+	–

Note: if the solvent of the positive control substance differed from the solvent of the test item, both solvents were run in the assay.

11.6. Experimental Method

The experimental methods were conducted according to the methods described by Ames et al. [1] and Maron and Ames [2], Kier et al. [3], Venitt and Parry [4], OECD Guideline No. 471, 2020 [5], Commission Regulation (EC) No. 440/2008, 2008 [6], EPA Guidelines, OPPTS 870.5100, 1998, 1996 [7][8] and according to the relevant SOPs of (b) (4)

11.7. Procedure for Exposure in the Assay 3

Assay 3 followed the standard plate incorporation procedure. Bacteria (cultured in Nutrient Broth No.2 as described in Section 10.1.6.) were exposed to the test item both in the presence and absence of an appropriate metabolic activation system.

(b) (4)

11.8. Procedure for Exposure in the Assay 4

Assay 4 followed the standard pre-incubation procedure [1][2][5][6][7][8] since no biologically relevant increase in the number of revertant colonies was observed in the Assay 3 (see details in Section 16.).

(b) (4)

12. EVALUATION OF THE RESULT

The colony numbers on the untreated / negative (solvent) / positive control and test item treated plates were determined by manual counting. Visual examination of the plates was also performed; precipitation or signs of growth inhibition (if any) were recorded and reported. The mean number of revertants per plate, the standard deviation and the mutation factor* values were calculated for each concentration level of the test item and for the controls using Microsoft Excel™ software.

* Mutation factor (MF): mean number of revertants on the test item plate / mean number of revertants on the vehicle control plate.

12.1. Criteria for Validity

The study was considered valid if:

- the number of revertant colonies of the negative (vehicle/solvent) and positive controls are in the relevant historical control range, generated at the test facility, in all tester strains of the main tests (with or without S9-mix);
- at least five analysable concentrations are presented in all strains of the main tests.
- the highest tested concentration should be at the limit test concentration, or the highest acceptable concentration based on cytotoxicity and/or precipitation.

12.2. Criteria for a Positive Response

A test item is considered mutagenic if:

- a dose–related increase in the number of revertants occurs and/or;
- a reproducible biologically relevant positive response for at least one of the dose groups occurs in at least one strain with or without metabolic activation.

An increase is considered biologically relevant if:

- the number of reversions is more than two times higher than the reversion rate of the negative (solvent) control in all *Salmonella typhimurium*

According to the guidelines [5][6][7][8], statistical method may be used as an aid in evaluating the test results. However, statistical significance should not be the only determining factor for a positive response.

12.3. Criteria for a Negative Response

A test article is considered non-mutagenic if it produces neither a concentration-related increase in the number of revertants nor a reproducible biologically relevant positive response at any of the concentration groups, with or without metabolic activation.Computerized Systems

The following computerized system was used in the study.

13. COMPUTERIZED SYSTEMS

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
(b) (4)	test item receipt

14. ARCHIVES

The study documents and samples:

- study plan and amendment,
- all raw data,
- retained sample of the test item and positive controls,
- correspondence,
- study report and any amendments

will be stored for 15 years after finalisation of the report in the Archives of (b) (4), (b) (6)) according to the Hungarian GLP regulation [9] and to Test Facility SOPs.

After the retention time has elapsed, all the archived materials listed above would be offered to the Sponsor or retained for a further period if agreed by a contract. No raw data or material relating to the study will be discarded without the Sponsor's prior written consent.

15. DEVIATIONS TO THE STUDY PLAN

There were no deviations to the Study Plan.

16. RESULTS AND DISCUSSION

16.1. Preliminary Range Finding Test

In the Preliminary Range Finding Test, the plate incorporation method was used. The preliminary test was performed using *Salmonella typhimurium* (b) (4) and *Salmonella typhimurium* (b) (4) tester strains in the presence and absence of metabolic activation system (±S9 Mix) with appropriate untreated, negative (solvent) and positive controls. Each sample (including the controls) was tested in triplicate.

Following concentrations were examined: (b) (4) and (b) (4) µg/plate.

Precipitate / slight precipitate was detected on the plates in the preliminary experiment in both examined bacterial strains with and without metabolic activation at (b) (4) and (b) (4) µg/plate concentration.

Inhibitory, cytotoxic effect of the test item (reduced / slightly reduced background lawn development) was observed in in the preliminary experiment in both examined bacterial strains with and without metabolic activation at (b) (4) and/or (b) (4) and (b) (4) µg/plate concentration.

The experimental results (revertant colony numbers per plate, mutation factors and standard deviations) are detailed in Table 1 and in Table 4.

16.2. Mutagenicity Tests (Assay 3 and Assay 4)

In Assay 3, the plate incorporation method was used. In Assay 4 the pre-incubation method was used. The assays were carried out using four *Salmonella typhimurium* strains ((b) (4) strain. The assays were performed in the presence and absence of a metabolic activation system. Each test was performed with appropriate untreated, negative (solvent) and positive controls. In the main tests each sample (including the controls) was tested in triplicate.

Based on the results of the preliminary experiment, the examined test concentrations in Assay 3 were (b) (4) and (b) µg/plate and in Assay 4 were (b) (4).81, (b) and (b) (4) µg/plate.

Precipitate/ slight precipitate was detected on the plates in Assay 3 in all examined bacterial strains with and without metabolic activation at (b) (4) and (b) (4) µg/plate concentrations.

Precipitate/ slight precipitate was detected on the plates in the Assay 4 in all examined bacterial strains with and without metabolic activation at (b) (4) µg/plate concentration and in *Salmonella typhimurium* (b) (4) bacterial strains with and without metabolic activation at (b) (4) µg/plate concentration and in *Salmonella typhimurium* (b) (4) and (b) (4) bacterial strains with and without metabolic activation at (b) (4) µg/plate concentration.

Inhibitory, cytotoxic effect of the test item (reduced/ slight reduced background lawn development) was observed in the Assay 3 in the examined bacterial strains with and without metabolic activation at (b) (4) µg/plate concentration.

Inhibitory, cytotoxic effect of the test item (reduced/ slight reduced background lawn development) was observed in the Assay 4 in the examined bacterial strains with and without metabolic activation at (b) (4) µg/plate concentration and in *Salmonella typhimurium* (b) (4) bacterial strain without metabolic activation at (b) (4) µg/plate concentration.

In Assay 3 (plate incorporation), the highest revertant rate was observed in *Salmonella typhimurium* (b) (4) bacterial strain at (b) (4) µg/plate concentration with metabolic activation (the observed mutation factor value was: MF: 2.02). However, there was no dose-response relationship, the observed mutation factor values were below the biologically relevant threshold limit and the number of revertant colonies was within the historical control range.

In Assay 4 (pre-incubation method), the highest revertant rate was observed in *Salmonella typhimurium* (b) (4) bacterial strain at (b) (4) µg/plate concentration with metabolic activation and in *Salmonella typhimurium* (b) (4) bacterial strain at (b) (4) and (b) (4) µg/plate concentration without metabolic activation (the observed mutation factor value was: MF: 1.29). However, there was no dose-response relationship, the observed mutation factor values were below the biologically relevant threshold limit and the number of revertant colonies was within the historical control range.

Higher numbers of revertant colonies compared to the vehicle (solvent) control were detected in the main tests in some other sporadic cases. However, no dose-dependence was observed in those cases and they were below the biologically relevant threshold value. The numbers of revertant colonies were within the historical control range in each case, so they were considered as reflecting the biological variability of the test.

In the main assays the number of revertant colonies did not show any biologically relevant increase compared to the solvent controls. There were no reproducible dose-related trends and there was no indication of any treatment-related effect.

The experimental results (revertant colony numbers per plate, mutation factors, and standard deviations) are summarized in Tables 2 and 3 and Tables 5 and 6.

16.3. Validity of the Tests

Untreated, negative (vehicle/solvent) and positive controls were run concurrently. The mean values of revertant colony numbers of untreated, negative (solvent) and positive control plates were within the historical control range in all strains. At least five analysable concentrations, up to an acceptable maximal concentration, were presented in all strains with and without metabolic activation.

Note: Salmonella typhimurium TA102 bacterial strain data of the untreated and DMSO controls in the Assay 4 were slightly lower than the bottom limit of the historical control range.

This fact has no impact on the results or integrity of the study since the control materials showed clear negative effects.

The reference mutagens showed a distinct increase of induced revertant colonies in each strain with and without metabolic activation. The viability of the bacterial cells was checked by a plating experiment in each test. The study was considered to be valid.

17. CONCLUSION

The test item was tested for potential mutagenic activity using the Bacterial Reverse Mutation Assay.

The experiments were carried out using histidine-requiring auxotroph strains of *Salmonella typhimurium* (*S. typhimurium* (b) (4)) in the presence and absence of a metabolic activation system, which was a cofactor-supplemented post-mitochondrial S9 fraction prepared from the livers of phenobarbital/β-naphthoflavone-induced rats.

The reported data of this mutagenicity assay show that under the experimental conditions applied the test item **did not induce gene mutations by base pair changes or frameshifts or cross-linking in the genome of the strains used.**

In conclusion, the test item L-tryptophan (TRP Pro) (Batch number: (b) (4)) had no mutagenic activity on the growth of the bacterial strains under the test conditions used in this study.

18. DISTRIBUTION OF THE FINAL REPORT

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19. REFERENCES

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T A B L E S

Table 1
Summary Result of the Range Finding Test

Concentrations (µg/plate)	Mean values of revertants / Mutation factor (MF)	*Salmonella typhimurium* tester strains			
		(b) (4)			
		-S9	+S9	-S9	+S9
Untreated control	Mean	19.0	21.0	86.3	90.3
	MF	1.00	1.05	1.03	0.97
DMSO control	Mean	19.0	20.0	--	89.3
	MF	1.00	1.00	--	0.96
Distilled water control	Mean	--	--	87.0	--
	MF	--	--	1.04	--
Distilled water 100µL control	Mean	19.0	20.0	83.7	92.7
	MF	1.00	1.00	1.00	1.00
(b) (4)	Mean	22.7	22.3	95.5	109.0
	MF	1.19	1.12	1.14	1.18
	Mean	21.7	24.3	108.5	91.0
	MF	1.14	1.22	1.30	0.98
	Mean	20.7	22.0	103.3	96.3
	MF	1.09	1.10	1.24	1.04
	Mean	19.3	21.0	80.7	84.3
	MF	1.02	1.05	0.96	0.91
	Mean	20.7	19.3	81.7	86.0
	MF	1.09	0.97	0.98	0.93
	Mean	19.3	19.7	87.0	90.7
	MF	1.02	0.98	1.04	0.98
	Mean	20.0	20.3	97.7	83.7
	MF	1.05	1.02	1.17	0.90
	Mean	405.3	--	--	--
	MF	21.33	--	--	--
	Mean	--	2438.7	--	2490.7
	MF	--	121.93	--	27.88
(b) (4)	Mean	--	--	1068.0	--
	MF	--	--	12.28	--

Table 2
Summary Result of the Assay 3

Concentrations (µg/plate)	Mean values of revertants / Mutation factor (MF)	*Salmonella typhimurium* tester strains									
		(b) (4)									
		-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Untreated control	Mean	31.0	23.7	109.3	106.7	288.7	292.0	13.7	14.7	11.7	9.7
	MF	1.11	1.27	1.11	1.03	1.01	0.99	1.05	1.13	1.21	0.76
DMSO control	Mean	30.0	24.3	--	98.3	--	292.7	--	13.7	10.3	10.7
	MF	1.07	1.30	--	0.95	--	1.00	--	1.05	1.07	0.84
Distilled water control	Mean	--	--	97.7	--	288.7	--	14.3	--	--	--
	MF	--	--	0.99	--	1.01	--	1.10	--	--	--
Distilled water 100µL control	Mean	28.0	18.7	98.7	104.0	285.3	294.0	13.0	13.0	9.7	12.7
	MF	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
(b) (4)	Mean	27.3	32.3	120.3	153.0	284.0	343.3	13.0	14.0	16.3	13.7
	MF	0.98	1.73	1.22	1.47	1.00	1.17	1.00	1.08	1.69	1.08
	Mean	22.3	26.3	99.3	128.3	290.0	300.7	11.3	14.7	7.7	10.3
	MF	0.80	1.41	1.01	1.23	1.02	1.02	0.87	1.13	0.79	0.82
	Mean	22.3	37.7	102.3	104.0	286.7	296.0	13.3	12.7	11.3	11.3
	MF	0.80	2.02	1.04	1.00	1.00	1.01	1.03	0.97	1.17	0.89
	Mean	18.3	26.7	103.0	105.3	288.7	293.3	12.0	13.3	10.0	10.0
	MF	0.65	1.43	1.04	1.01	1.01	1.00	0.92	1.03	1.03	0.79
	Mean	21.0	29.7	104.3	110.3	291.3	342.0	12.0	11.0	10.0	9.3
	MF	0.75	1.59	1.06	1.06	1.02	1.16	0.92	0.85	1.03	0.74
	Mean	21.0	29.7	95.7	118.3	284.0	325.3	11.0	13.0	10.7	8.7
	MF	0.75	1.59	0.97	1.14	1.00	1.11	0.85	1.00	1.10	0.68
	Mean	24.7	28.3	87.3	108.3	290.7	330.0	12.0	12.7	10.3	10.0
	MF	0.88	1.52	0.89	1.04	1.02	1.12	0.92	0.97	1.07	0.79
	Mean	416.0	--	--	--	--	--	--	--	--	--
	MF	13.87	--	--	--	--	--	--	--	--	--
	Mean	--	2481.3	--	2476.0	--	--	--	202.0	--	192.7
	MF	--	101.97	--	25.18	--	--	--	14.78	--	18.06
	Mean	--	--	--	--	--	1052.0	--	--	--	--
	MF	--	--	--	--	--	3.59	--	--	--	--
	Mean	--	--	1090.7	--	--	--	1085.3	--	--	--
	MF	--	--	11.17	--	--	--	75.72	--	--	--
	Mean	--	--	--	--	858.7	--	--	--	--	--
	MF	--	--	--	--	2.97	--	--	--	--	--
	Mean	--	--	--	--	--	--	--	--	449.3	--
	MF	--	--	--	--	--	--	--	--	43.48	--

Table 3
Summary Result of the Assay 4

Concentrations (µg/plate)	Mean values of revertants / Mutation factor (MF)	*Salmonella typhimurium* tester strains									
		TA 98		TA 100		TA 102		TA 1535		TA 1537	
		-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Untreated control	Mean	17.7	19.3	88.7	88.7	282.7	294.0	13.0	13.3	9.7	8.3
	MF	0.90	0.88	1.11	0.94	1.00	1.00	1.03	0.98	1.04	0.96
DMSO control	Mean	18.7	21.7	--	94.7	--	301.3	--	14.0	9.0	8.7
	MF	0.95	0.98	--	1.01	--	1.02	--	1.02	0.96	1.00
Distilled water control	Mean	--	--	94.0	--	288.0	--	12.3	--	--	--
	MF	--	--	1.18	--	1.02	--	0.97	--	--	--
Distilled water 100µL control	Mean	19.7	22.0	79.7	94.0	282.7	294.7	12.7	13.7	9.3	8.7
	MF	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
(b) (4)	Mean	18.7	22.7	87.0	121.0	267.3	296.7	12.0	12.7	10.0	9.3
	MF	0.95	1.03	1.09	1.29	0.95	1.01	0.95	0.93	1.07	1.08
	Mean	18.3	20.3	85.7	102.0	284.0	290.0	12.0	11.7	11.0	9.3
	MF	0.93	0.92	1.08	1.09	1.00	0.98	0.95	0.85	1.18	1.08
	Mean	18.7	20.3	96.3	96.3	275.3	290.0	12.7	11.3	12.0	9.3
	MF	0.95	0.92	1.21	1.02	0.97	0.98	1.00	0.83	1.29	1.08
	Mean	18.7	18.7	83.0	97.7	276.0	298.7	12.3	12.3	12.0	9.0
	MF	0.95	0.85	1.04	1.04	0.98	1.01	0.97	0.90	1.29	1.04
	Mean	16.3	20.7	82.3	85.0	270.0	291.3	13.3	12.0	11.0	7.7
	MF	0.83	0.94	1.03	0.90	0.96	0.99	1.05	0.88	1.18	0.88
	Mean	18.7	18.7	89.3	90.3	286.0	294.0	13.0	12.3	8.3	10.0
	MF	0.95	0.85	1.12	0.96	1.01	1.00	1.03	0.90	0.89	1.15
	Mean	17.0	19.3	89.0	96.0	270.0	277.3	13.3	11.3	9.7	8.7
	MF	0.86	0.88	1.12	1.02	0.96	0.94	1.05	0.83	1.04	1.00
		18.0	19.7	96.0	86.7	272.7	298.7	13.7	11.3	9.0	8.7
		0.92	0.89	1.21	0.92	0.96	1.01	1.08	0.83	0.96	1.00
	Mean	405.3	--	--	--	--	--	--	--	--	--
	MF	21.71	--	--	--	--	--	--	--	--	--
	Mean	--	2434.7	--	2488.0	--	--	--	203.7	--	216.0
	MF	--	112.37	--	26.28	--	--	--	14.55	--	24.92
	Mean	--	--	--	--	--	993.3	--	--	--	--
	MF	--	--	--	--	--	3.30	--	--	--	--
	Mean	--	--	1208.0	--	--	--	1233.3	--	--	--
	MF	--	--	12.85	--	--	--	100.00	--	--	--
	Mean	--	--	--	--	1038.7	--	--	--	--	--
	MF	--	--	--	--	3.61	--	--	--	--	--
	Mean	--	--	--	--	--	--	--	--	404.0	--
	MF	--	--	--	--	--	--	--	--	44.89	--

Table 4
Result of Pre-Experiment for Toxicity (Informatory Toxicity Test)

Test Item: L-tryptophan (TRP Pro)
Date: 11–13 January 2022
Strain: *Salmonella typhimurium* TA98
Cell count (overnight culture): 1.77 x 10^9 CFU/mL

Concentration: (µg/plate)		Revertant colony number -S9	Revertant colony number +S9
[redacted]		20 R,P	20 R,P
		24 R,P	23 R,P
		24 R,P	24 R,P
	Mean	**22.7**	**22.3**
	SD	**2.31**	**2.08**
	MF	**1.19**	**1.12**
[redacted]		19 SR,SP	24 SR,SP
		23 SR,SP	24 SR,SP
		23 SR,SP	25 SR,SP
	Mean	**21.7**	**24.3**
	SD	**2.31**	**0.58**
	MF	**1.14**	**1.22**
[redacted]		20 SR	22 SR
		21 SR	23 SR
		21 SR	21 SR
	Mean	**20.7**	**22.0**
	SD	**0.58**	**1.00**
	MF	**1.09**	**1.10**
[redacted]		20	20
		20	21
		18	22
	Mean	**19.3**	**21.0**
	SD	**1.15**	**1.00**
	MF	**1.02**	**1.05**
[redacted]		19	19
		22	19
		21	20
	Mean	**20.7**	**19.3**
	SD	**1.53**	**0.58**
	MF	**1.09**	**0.97**
[redacted]		19	19
		18	20
		21	20
	Mean	**19.3**	**19.7**
	SD	**1.53**	**0.58**
	MF	**1.02**	**0.98**
[redacted]		21	19
		19	21
		20	21
	Mean	**20.0**	**20.3**
	SD	**1.00**	**1.15**
	MF	**1.05**	**1.02**

Concentration: (µg/plate)		Revertant colony number -S9	Revertant colony number +S9
Untreated control		19	20
		18	20
		20	23
	Mean	**19.0**	**21.0**
	SD	**1.00**	**1.73**
	MF	**1.00**	**1.05**
DMSO control*		20	20
		19	19
		18	21
	Mean	**19.0**	**20.0**
	SD	**1.00**	**1.00**
	MF	**1.00**	**1.00**
Distilled water 100µL control		20	18
		20	21
		17	21
	Mean	**19.0**	**20.0**
	SD	**1.73**	**1.73**
	MF	**1.00**	**1.00**
Positive control NPD (4 µg)		420	**2AA (2 µg)** 2440
		392	2420
		404	2456
	Mean	**405.3**	**2438.7**
	SD	**14.05**	**18.04**
	MF	**21.33**	**121.93**

R: Reduced background lawn development
SR: Slightly reduced background lawn development
P: Precipitate
SP: Slight precipitate
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of NPD and 2AA

Test Facility Study Code:

Table 4 (continued)
Result of Pre-Experiment for Toxicity (Informatory Toxicity Test)

Test Item: L-tryptophan (TRP Pro)
Date: 11–13 January 2022
Strain: *Salmonella typhimurium* TA100
Cell count (overnight culture): 2.12 x 10^9 CFU/mL

Concentration: (µg/plate)	Revertant colony number -S9	Revertant colony number +S9
(b) (4)	98 R,P	107 R,P
	93 R,P	112 R,P
	infected	108 R,P
Mean	**95.5**	**109.0**
SD	**3.06**	**2.65**
MF	**1.14**	**1.18**
(b) (4)	infected	92 SR,SP
	110 SR,SP	94 SR,SP
	107 SR,SP	87 SR,SP
Mean	**108.5**	**91.0**
SD	**1.84**	**3.61**
MF	**1.30**	**0.98**
(b) (4)	107 SR	76 SR
	102 SR	99 SR
	101 SR	114 SR
Mean	**103.3**	**96.3**
SD	**3.21**	**19.14**
MF	**1.24**	**1.04**
(b) (4)	76	89
	88	91
	78	73
Mean	**80.7**	**84.3**
SD	**6.43**	**9.87**
MF	**0.96**	**0.91**
(b) (4)	81	85
	82	86
	82	87
Mean	**81.7**	**86.0**
SD	**0.58**	**1.00**
MF	**0.98**	**0.93**
(b) (4)	80	73
	89	106
	92	93
Mean	**87.0**	**90.7**
SD	**6.24**	**16.62**
MF	**1.04**	**0.98**
(b) (4)	98	101
	99	79
	96	71
Mean	**97.7**	**83.7**
SD	**1.53**	**15.53**
MF	**1.17**	**0.90**

Concentration: (µg/plate)	Revertant colony number -S9		Revertant colony number +S9
Untreated control	90		91
	91		94
	78		86
Mean	**86.3**		**90.3**
SD	**7.23**		**4.04**
MF	**1.03**		**0.97**
DMSO control*	84		82
	82		90
	84		96
Mean	**83.3**		**89.3**
SD	**1.15**		**7.02**
MF	**1.00**		**0.96**
Distilled water	80		88
100µL control	85		100
	86		90
Mean	**83.7**		**92.7**
SD	**3.21**		**6.43**
MF	**1.00**		**1.00**
Distilled water	92		96
Control**	88		94
	81		86
Mean	**87.0**		**92.0**
SD	**5.57**		**5.29**
MF	**1.04**		**0.99**
Positive control	1032	**2AA**	2464
SAZ	1092	**(2 µg)**	2496
(2 µg)	1080		2512
Mean	**1068.0**		**2490.7**
SD	**31.75**		**24.44**
MF	**12.28**		**27.88**

R: Reduced background lawn development
SR: Slightly reduced background lawn development
P: Precipitate
SP: Slight precipitate
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of 2AA

**Distilled water control was used because of SAZ

Test Facility Study Code:

Table 5
Result of Assay 3 (Plate Incorporation Method)

Test Item: L-tryptophan (TRP Pro)
Date: 23–25 February 2022
Strain: *Salmonella typhimurium* TA98
Cell count (overnight culture): 1.75 x 10^9 CFU/mL

Concentration: (µg/plate)	Revertant colony number -S9	Revertant colony number +S9
(b) (4)	22 P,R	32 P,R
	35 P,R	36 P,R
	25 P,R	29 P,R
Mean	**27.3**	**32.3**
SD	**6.81**	**3.51**
MF	**0.98**	**1.73**
(b) (4)	23 SP	25 SP
	22 SP	18 SP
	22 SP	36 SP
Mean	**22.3**	**26.3**
SD	**0.58**	**9.07**
MF	**0.80**	**1.41**
(b) (4)	16	32
	25	36
	26	45
Mean	**22.3**	**37.7**
SD	**5.51**	**6.66**
MF	**0.80**	**2.02**
(b) (4)	18	25
	20	33
	17	22
Mean	**18.3**	**26.7**
SD	**1.53**	**5.69**
MF	**0.65**	**1.43**
(b) (4)	20	31
	25	33
	18	25
Mean	**21.0**	**29.7**
SD	**3.61**	**4.16**
MF	**0.75**	**1.59**
(b) (4)	28	24
	20	36
	15	29
Mean	**21.0**	**29.7**
SD	**6.56**	**6.03**
MF	**0.75**	**1.59**
(b)	31	24
	19	17
	24	44
Mean	**24.7**	**28.3**
SD	**6.03**	**14.01**
MF	**0.88**	**1.52**

Concentration: (µg/plate)	Revertant colony number -S9	Revertant colony number +S9
Untreated control	35	22
	30	26
	28	23
Mean	**31.0**	**23.7**
SD	**3.61**	**2.08**
MF	**1.11**	**1.27**
DMSO control*	29	25
	36	17
	25	31
Mean	**30.0**	**24.3**
SD	**5.57**	**7.02**
MF	**1.07**	**1.30**
Distilled water	31	18
100µL control	30	17
	23	21
Mean	**28.0**	**18.7**
SD	**4.36**	**2.08**
MF	**1.00**	**1.00**
Positive control	392	**2AA** 2484
NPD	416	**(2 µg)** 2500
(4 µg)	440	2460
Mean	**416.0**	**2481.3**
SD	**24.00**	**20.13**
MF	**13.87**	**101.97**

P: Precipitate
R: Reduced background lawn development
SP: Slight precipitate
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of NPD and 2AA

Table 5 (continued)
Result of Assay 3 (Plate Incorporation Method)

Test Item: L-tryptophan (TRP Pro)
Date: 23–25 February 2022
Strain: *Salmonella typhimurium* TA100
Cell count (overnight culture): 2.57 x 10^9 CFU/mL

Concentration: (µg/plate)		Revertant colony number -S9		Revertant colony number +S9		Concentration: (µg/plate)		Revertant colony number -S9		Revertant colony number +S9	
(b) (4)		126	P,R	165	P,R	**Untreated control**		116		104	
		108	P,R	149	P,R			110		100	
		127	P,R	145	P,R			102		116	
	Mean	**120.3**		**153.0**			**Mean**	**109.3**		**106.7**	
	SD	**10.69**		**10.58**			**SD**	**7.02**		**8.33**	
	MF	**1.22**		**1.47**			**MF**	**1.11**		**1.03**	
(b) (4)		101	SP	146	SP	**DMSO control***		93		84	
		108	SP	127	SP			103		103	
		89	SP	112	SP			125		108	
	Mean	**99.3**		**128.3**			**Mean**	**107.0**		**98.3**	
	SD	**9.61**		**17.04**			**SD**	**16.37**		**12.66**	
	MF	**1.01**		**1.23**			**MF**	**1.08**		**0.95**	
(b) (4)		108		127		**Distilled water**		91		105	
		112		96		**Control****		106		117	
		87		89				96		106	
	Mean	**102.3**		**104.0**			**Mean**	**97.7**		**109.3**	
	SD	**13.43**		**20.22**			**SD**	**7.64**		**6.66**	
	MF	**1.04**		**1.00**			**MF**	**0.99**		**1.05**	
(b) (4)		118		133		**Distilled water**		108		112	
		95		98		**100µL Control**		89		99	
		96		85				99		101	
	Mean	**103.0**		**105.3**			**Mean**	**98.7**		**104.0**	
	SD	**13.00**		**24.83**			**SD**	**9.50**		**7.00**	
	MF	**1.04**		**1.01**			**MF**	**1.00**		**1.00**	
(b) (4)		99		119		**Positive control**		1092	**2AA**	2460	
		98		120		**SAZ**		1120	**(2 µg)**	2480	
		116		92		**(2 µg)**		1060		2488	
	Mean	**104.3**		**110.3**			**Mean**	**1090.7**		**2476.0**	
	SD	**10.12**		**15.89**			**SD**	**30.02**		**14.42**	
	MF	**1.06**		**1.06**			**MF**	**11.17**		**25.18**	
(b) (4)		99		115							
		85		129							
		103		111							
	Mean	**95.7**		**118.3**							
	SD	**9.45**		**9.45**							
	MF	**0.97**		**1.14**							
(b)		86		93							
		101		111							
		75		121							
	Mean	**87.3**		**108.3**							
	SD	**13.05**		**14.19**							
	MF	**0.89**		**1.04**							

P: Precipitate
R: Reduced background lawn development
SP: Slight precipitate
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of 2AA
**Distilled water control was used because of SAZ

Table 5 (continued)
Result of Assay 3 (Plate Incorporation Method)

Test Item: L-tryptophan (TRP Pro)
Date: 23–25 February 2022
Strain: *Salmonella typhimurium* TA102
Cell count (overnight culture): 3.61 x 10^9 CFU/mL

Concentration: (µg/plate)		Revertant colony number -S9		Revertant colony number +S9		Concentration: (µg/plate)		Revertant colony number -S9		Revertant colony number +S9	
(b) (4)		296	SR,P	356	SR,P	**Untreated control**		278		294	
		280	SR,P	332	SR,P			296		286	
		276	SR,P	342	SR,P			292		296	
	Mean	**284.0**		**343.3**			**Mean**	**288.7**		**292.0**	
	SD	**10.58**		**12.06**			**SD**	**9.45**		**5.29**	
	MF	**1.00**		**1.17**			**MF**	**1.01**		**0.99**	
(b) (4)		286	SP	306	SP	**DMSO control***		294		296	
		294	SP	268	SP			290		290	
		290	SP	328	SP			280		292	
	Mean	**290.0**		**300.7**			**Mean**	**288.0**		**292.7**	
	SD	**4.00**		**30.35**			**SD**	**7.21**		**3.06**	
	MF	**1.02**		**1.02**			**MF**	**1.01**		**1.00**	
(b) (4)		280		300		**Distilled water**		290		300	
		288		302		**Control****		286		288	
		292		286				290		292	
	Mean	**286.7**		**296.0**			**Mean**	**288.7**		**293.3**	
	SD	**6.11**		**8.72**			**SD**	**2.31**		**6.11**	
	MF	**1.00**		**1.01**			**MF**	**1.01**		**1.00**	
(b) (4)		288		310		**Distilled water**		280		296	
		294		286		**100 µL control**		286		290	
		284		284				290		296	
	Mean	**288.7**		**293.3**			**Mean**	**285.3**		**294.0**	
	SD	**5.03**		**14.47**			**SD**	**5.03**		**3.46**	
	MF	**1.01**		**1.00**			**MF**	**1.00**		**1.00**	
(b) (4)		294		340		**Positive control**		884	**2AA**	1100	
		286		316		**Mitomycin C**		832	**(10 µg)**	1004	
		294		370		**(2.5 µg)**		860		1052	
	Mean	**291.3**		**342.0**			**Mean**	**858.7**		**1052.0**	
	SD	**4.62**		**27.06**			**SD**	**26.03**		**48.00**	
	MF	**1.02**		**1.16**			**MF**	**2.97**		**3.59**	
(b) (4)		278		314							
		290		364							
		284		298							
	Mean	**284.0**		**325.3**							
	SD	**6.00**		**34.43**							
	MF	**1.00**		**1.11**							
(b)		292		352							
		294		286							
		286		352							
	Mean	**290.7**		**330.0**							
	SD	**4.16**		**38.11**							
	MF	**1.02**		**1.12**							

P: Precipitate
SP: Slight precipitate
SR: Slightly reduced background lawn
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of 2AA
**Distilled water control was used because of Mitomycin C

Test Facility Study Code:

Table 5 (continued)
Result of Assay 3 (Plate Incorporation Method)

Test Item: L-tryptophan (TRP Pro)
Date: 23–25 February 2022
Strain: *Salmonella typhimurium* TA1535
Cell count (overnight culture): 1.76 x 10^9 CFU/mL

Concentration: (µg/plate)	Revertant colony number -S9	Revertant colony number +S9
(b) (4)	12 R,P	9 R,P
	12 R,P	17 R,P
	15 R,P	16 R,P
	Mean 13.0	**14.0**
	SD 1.73	**4.36**
	MF 1.00	**1.08**
(b) (4)	10 SP	13 SP
	13 SP	15 SP
	11 SP	16 SP
	Mean 11.3	**14.7**
	SD 1.53	**1.53**
	MF 0.87	**1.13**
(b) (4)	10	12
	16	13
	14	13
	Mean 13.3	**12.7**
	SD 3.06	**0.58**
	MF 1.03	**0.97**
(b) (4)	11	14
	10	16
	15	10
	Mean 12.0	**13.3**
	SD 2.65	**3.06**
	MF 0.92	**1.03**
(b) (4)	14	6
	10	14
	12	13
	Mean 12.0	**11.0**
	SD 2.00	**4.36**
	MF 0.92	**0.85**
(b) (4)	10	16
	10	13
	13	10
	Mean 11.0	**13.0**
	SD 1.73	**3.00**
	MF 0.85	**1.00**
(b)	12	16
	11	12
	13	10
	Mean 12.0	**12.7**
	SD 1.00	**3.06**
	MF 0.92	**0.97**

Concentration: (µg/plate)	Revertant colony number -S9	Revertant colony number +S9
Untreated control	13	13
	13	16
	15	15
Mean	**13.7**	**14.7**
SD	**1.15**	**1.53**
MF	**1.05**	**1.13**
DMSO control*	13	11
	11	15
	16	15
Mean	**13.3**	**13.7**
SD	**2.52**	**2.31**
MF	**1.03**	**1.05**
Distilled water Control**	12	15
	15	13
	16	14
Mean	**14.3**	**14.0**
SD	**2.08**	**1.00**
MF	**1.10**	**1.08**
Distilled water 100 µL control	12	13
	12	12
	15	14
Mean	**13.0**	**13.0**
SD	**1.73**	**1.00**
MF	**1.00**	**1.00**
Positive control SAZ (2 µg)	1120	**2AA (2 µg)** 197
	1052	201
	1084	208
Mean	**1085.3**	**202.0**
SD	**34.02**	**5.57**
MF	**75.72**	**14.78**

P: Precipitate
R: Reduced background lawn development
SP: Slight precipitate
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of 2AA
**Distilled water control was used because of SAZ

Table 5 (continued)
Result of Assay 3 (Plate Incorporation Method)

Test Item: L-tryptophan (TRP Pro)
Date: 23–25 February 2022
Strain: *Salmonella typhimurium* TA1537
Cell count (overnight culture): 1.33 x 10^9 CFU/mL

Concentration: (µg/plate)		Revertant colony number -S9		Revertant colony number +S9		Concentration: (µg/plate)		Revertant colony number -S9		Revertant colony number +S9	
(b) (4)		15	R,P	13	R,P	**Untreated control**		13		10	
		15	R,P infected	14	R,P			12		7	
		19	R,P	14	R,P			10		12	
	Mean	**16.3**		**13.7**			**Mean**	**11.7**		**9.7**	
	SD	**2.31**		**0.58**			**SD**	**1.53**		**2.52**	
	MF	**1.69**		**1.08**			**MF**	**1.21**		**0.76**	
(b) (4)		6	SP	15	SP	**DMSO control***		8		10	
		13	SP	7	SP			11		12	
		4	SP	9	SP			12		10	
	Mean	**7.7**		**10.3**			**Mean**	**10.3**		**10.7**	
	SD	**4.73**		**4.16**			**SD**	**2.08**		**1.15**	
	MF	**0.79**		**0.82**			**MF**	**1.07**		**0.84**	
(b) (4)		12		9		**Distilled water**		10		10	
		11		15		**100 µL control**		8		13	
		11		10				11		15	
	Mean	**11.3**		**11.3**			**Mean**	**9.7**		**12.7**	
	SD	**0.58**		**3.21**			**SD**	**1.53**		**2.52**	
	MF	**1.17**		**0.89**			**MF**	**1.00**		**1.00**	
(b) (4)		9		13		**Positive control**		440	**2AA**	204	
		10		10		**9AA**		424	**(2 µg)**	198	
		11		7		**(50 µg)**		484		176	
	Mean	**10.0**		**10.0**			**Mean**	**449.3**		**192.7**	
	SD	**1.00**		**3.00**			**SD**	**31.07**		**14.74**	
	MF	**1.03**		**0.79**			**MF**	**43.48**		**18.06**	
(b) (4)		10		11							
		9		7							
		11		10							
	Mean	**10.0**		**9.3**							
	SD	**1.00**		**2.08**							
	MF	**1.03**		**0.74**							
(b) (4)		13		9							
		9		7							
		10		10							
	Mean	**10.7**		**8.7**							
	SD	**2.08**		**1.53**							
	MF	**1.10**		**0.68**							
(b)		9		9							
		10		10							
		12		11							
	Mean	**10.3**		**10.0**							
	SD	**1.53**		**1.00**							
	MF	**1.07**		**0.79**							

P: Precipitate
R: Reduced background lawn development
SP: Slight precipitate
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of 9AA and 2AA

Table 6
Result of Assay 4 (Pre-Incubation Method)

Test Item: L-tryptophan (TRP Pro)
Date: 01–03 March 2022
Strain: *Salmonella typhimurium* TA98
Cell count (overnight culture): 1.67 x 10^9 CFU/mL

Concentration: (µg/plate)		Revertant colony number -S9	Revertant colony number +S9
(b) (4)		17 P,R	20 P,R
		18 P,R	23 P,R
		21 P,R	25 P,R
	Mean	**18.7**	**22.7**
	SD	**2.08**	**2.52**
	MF	**0.95**	**1.03**
(b) (4)		17 P	19 P
		19 P	22 P
		19 P	20 P
	Mean	**18.3**	**20.3**
	SD	**1.15**	**1.53**
	MF	**0.93**	**0.92**
(b) (4)		17 SP	19 SP
		20 SP	20 SP
		19 SP	22 SP
	Mean	**18.7**	**20.3**
	SD	**1.53**	**1.53**
	MF	**0.95**	**0.92**
(b) (4)		17	17
		19	18
		20	21
	Mean	**18.7**	**18.7**
	SD	**1.53**	**2.08**
	MF	**0.95**	**0.85**
(b) (4)		16	21
		16	21
		17	20
	Mean	**16.3**	**20.7**
	SD	**0.58**	**0.58**
	MF	**0.83**	**0.94**
(b) (4)		16	18
		18	19
		22	19
	Mean	**18.7**	**18.7**
	SD	**3.06**	**0.58**
	MF	**0.95**	**0.85**
(b)		17	17
		17	20
		17	21
	Mean	**17.0**	**19.3**
	SD	**0.00**	**2.08**
	MF	**0.86**	**0.88**
(b) (4)		17	19
		18	19
		19	21
	Mean	**18.0**	**19.7**
	SD	**1.00**	**1.15**
	MF	**0.92**	**0.89**

Concentration: (µg/plate)		Revertant colony number -S9		Revertant colony number +S9
Untreated control		18		18
		17		20
		18		20
	Mean	**17.7**		**19.3**
	SD	**0.58**		**1.15**
	MF	**0.90**		**0.88**
DMSO control*		18		20
		18		22
		20		23
	Mean	**18.7**		**21.7**
	SD	**1.15**		**1.53**
	MF	**0.95**		**0.98**
Distilled water		18		21
100µL control		20		22
		21		23
	Mean	**19.7**		**22.0**
	SD	**1.53**		**1.00**
	MF	**1.00**		**1.00**
Positive control		388	**2AA**	2432
NPD		408	**(2 µg)**	2400
(4 µg)		420		2472
		405.3		**2434.7**
		16.17		**36.07**
		21.71		**112.37**

R: Reduced background lawn development
P: Precipitate
SP: Slight precipitate
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of NPD and 2AA

Test Facility Study Code:

Table 6 (continued)
Result of Assay 4 (Pre-Incubation Method)

Test Item: L-tryptophan (TRP Pro)
Date: 01–03 March 2022
Strain: *Salmonella typhimurium* TA100
Cell count (overnight culture): 2.09 x 10^9 CFU/mL

Concentration: (µg/plate)		Revertant colony number -S9		Revertant colony number +S9	
(b) (4)		86	R,P	106	P,R
		88	R,P	118	P,R
		87	R,P	139	P,R
	Mean	**87.0**		**121.0**	
	SD	**1.00**		**16.70**	
	MF	**1.09**		**1.29**	
(b) (4)		80	P,SR	102	P
		99	P,SR	105	P
		78	P,SR	99	P
	Mean	**85.7**		**102.0**	
	SD	**11.59**		**3.00**	
	MF	**1.08**		**1.09**	
(b) (4)		101	SP	99	SP
		90	SP	93	SP
		98	SP	97	SP
	Mean	**96.3**		**96.3**	
	SD	**5.69**		**3.06**	
	MF	**1.21**		**1.02**	
(b) (4)		82		96	
		76		98	
		91		99	
	Mean	**83.0**		**97.7**	
	SD	**7.55**		**1.53**	
	MF	**1.04**		**1.04**	
(b) (4)		78		92	
		89		82	
		80		81	
	Mean	**82.3**		**85.0**	
	SD	**5.86**		**6.08**	
	MF	**1.03**		**0.90**	
(b) (4)		82		88	
		97		86	
		89		97	
	Mean	**89.3**		**90.3**	
	SD	**7.51**		**5.86**	
	MF	**1.12**		**0.96**	
(b)		94		92	
		86		92	
		87		104	
	Mean	**89.0**		**96.0**	
	SD	**4.36**		**6.93**	
	MF	**1.12**		**1.02**	
(b) (4)		91		86	
		102		96	
		95		78	
	Mean	**96.0**		**86.7**	
	SD	**5.57**		**9.02**	
	MF	**1.21**		**0.92**	

Concentration: (µg/plate)		Revertant colony number -S9		Revertant colony number +S9	
Untreated control		88		85	
		105		89	
		73		92	
	Mean	**88.7**		**88.7**	
	SD	**16.01**		**3.51**	
	MF	**1.11**		**0.94**	
DMSO control*		86		90	
		80		98	
		71		96	
	Mean	**79.0**		**94.7**	
	SD	**7.55**		**4.16**	
	MF	**0.99**		**1.01**	
Distilled water Control**		103		124	
		83		93	
		96		99	
	Mean	**94.0**		**105.3**	
	SD	**10.15**		**16.44**	
	MF	**1.18**		**1.12**	
Distilled water 100 µL control		76		93	
		77		101	
		86		88	
	Mean	**79.7**		**94.0**	
	SD	**5.51**		**6.56**	
	MF	**1.00**		**1.00**	
Positive control SAZ (2 µg)		1184	**2AA**	2416	
		1196	**(2 µg)**	2608	
		1244		2440	
	Mean	**1208.0**		**2488.0**	
	SD	**31.75**		**104.61**	
	MF	**12.85**		**26.28**	

R: Reduced background lawn development
SR: Slightly reduced background lawn
P: Precipitate
SP: Slight precipitate
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of 2AA
**Distilled water control was used because of SAZ

Test Facility Study Code:

Table 6 (continued)
Result of Assay 4 (Pre-Incubation Method)

Test Item: L-tryptophan (TRP Pro)
Date: 01–03 March 2022
Strain: *Salmonella typhimurium* TA102
Cell count (overnight culture): 2.98 x 10^9 CFU/mL

Concentration: (µg/plate)		Revertant colony number -S9	Revertant colony number +S9
(b) (4)		264 P,R infected	298 P,R
		244 P,R	290 P,R
		294 P,R	302 P,R
	Mean	**267.3**	**296.7**
	SD	**25.17**	**6.11**
	MF	**0.95**	**1.01**
(b) (4)		278 P	282 P
		274 P	298 P
		300 P	290 P
	Mean	**284.0**	**290.0**
	SD	**14.00**	**8.00**
	MF	**1.00**	**0.98**
(b) (4)		272	300
		270	298
		284	272
	Mean	**275.3**	**290.0**
	SD	**7.57**	**15.62**
	MF	**0.97**	**0.98**
(b) (4)		292	308
		250	290
		286	298
	Mean	**276.0**	**298.7**
	SD	**22.72**	**9.02**
	MF	**0.98**	**1.01**
(b) (4)		260	302
		288	288
		262	284
	Mean	**270.0**	**291.3**
	SD	**15.62**	**9.45**
	MF	**0.96**	**0.99**
(b) (4)		264	280
		290	296
		304	306
	Mean	**286.0**	**294.0**
	SD	**20.30**	**13.11**
	MF	**1.01**	**1.00**
(b)		264	298
		266	270
		280	264
	Mean	**270.0**	**277.3**
	SD	**8.72**	**18.15**
	MF	**0.96**	**0.94**
(b) (4)		268	294
		278	298
		272	304
	Mean	**272.7**	**298.7**
	SD	**5.03**	**5.03**
	MF	**0.96**	**1.01**

Concentration: (µg/plate)		Revertant colony number -S9		Revertant colony number +S9
Untreated control		316		306
		260		310
		272		266
	Mean	**282.7**		**294.0**
	SD	**29.48**		**24.33**
	MF	**1.00**		**1.00**
DMSO control*		250		302
		336		286
		248		316
	Mean	**278.0**		**301.3**
	SD	**50.24**		**15.01**
	MF	**0.98**		**1.02**
Distilled water		292		302
Control**		280		296
		292		296
	Mean	**288.0**		**298.0**
	SD	**6.93**		**3.46**
	MF	**1.02**		**1.01**
Distilled water		246		294
100 µL control		296		290
		306		300
	Mean	**282.7**		**294.7**
	SD	**32.15**		**5.03**
	MF	**1.00**		**1.00**
Positive control		1024	**2AA**	992
Mitomycin C		1056	**(10 µg)**	960
(2.5 µg)		1036		1028
	Mean	**1038.7**		**993.3**
	SD	**16.17**		**34.02**
	MF	**3.61**		**3.30**

P: Precipitate
R: Reduced background lawn development
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of 2AA
**Distilled water control was used because of Mitomycin C

Test Facility Study Code:

Table 6 (continued)
Assay 4 (Pre-Incubation Method)

Test Item: L-tryptophan (TRP Pro)
Date: 01-03 March 2022
Strain: *Salmonella typhimurium* TA1535
Cell count (overnight culture): 2.07 x 10^9 CFU/mL

Concentration: (µg/plate)		Revertant colony number -S9	Revertant colony number +S9
(b) (4)		12 P,R	11 P,R
		12 P,R	13 P,R
		12 P,R	14 P,R
	Mean	**12.0**	**12.7**
	SD	**0.00**	**1.53**
	MF	**0.95**	**0.93**
(b) (4)		11	12
		11	11
		14	12
	Mean	**12.0**	**11.7**
	SD	**1.73**	**0.58**
	MF	**0.95**	**0.85**
(b) (4)		12	8
		13	12
		13	14
	Mean	**12.7**	**11.3**
	SD	**0.58**	**3.06**
	MF	**1.00**	**0.83**
(b) (4)		9	12
		14	12
		14	13
	Mean	**12.3**	**12.3**
	SD	**2.89**	**0.58**
	MF	**0.97**	**0.90**
(b) (4)		12	11
		13	12
		15	13
	Mean	**13.3**	**12.0**
	SD	**1.53**	**1.00**
	MF	**1.05**	**0.88**
(b) (4)		12	10
		13	14
		14	13
	Mean	**13.0**	**12.3**
	SD	**1.00**	**2.08**
	MF	**1.03**	**0.90**
(b)		12	11
		13	11
		15	12
	Mean	**13.3**	**11.3**
	SD	**1.53**	**0.58**
	MF	**1.05**	**0.83**
(b) (4)		14	11
		14	11
		13	12
	Mean	**13.7**	**11.3**
	SD	**0.58**	**0.58**
	MF	**1.08**	**0.83**

Concentration: (µg/plate)		Revertant colony number -S9		Revertant colony number +S9
Untreated control		12		13
		13		13
		14		14
	Mean	**13.0**		**13.3**
	SD	**1.00**		**0.58**
	MF	**1.03**		**0.98**
DMSO control*		12		13
		12		14
		12		15
	Mean	**12.0**		**14.0**
	SD	**0.00**		**1.00**
	MF	**0.95**		**1.02**
Distilled water		12		13
Control**		13		13
		12		15
	Mean	**12.3**		**13.7**
	SD	**0.58**		**1.15**
	MF	**0.97**		**1.00**
Distilled water		12		12
100 µL control		13		14
		13		15
	Mean	**12.7**		**13.7**
	SD	**0.58**		**1.53**
	MF	**1.00**		**1.00**
Positive control		1196	**2AA**	199
SAZ		1240	**(2 µg)**	207
(2 µg)		1264		205
	Mean	**1233.3**		**203.7**
	SD	**34.49**		**4.16**
	MF	**100.00**		**14.55**

R: Reduced background lawn development
P: Precipitate
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of 2AA
**Distilled water control was used because of SAZ

Test Facility Study Code:

Table 6 (continued)
Assay 4 (Pre-Incubation Method)

Test Item: L-tryptophan (TRP Pro)
Date: 01-03 March 2022
Strain: *Salmonella typhimurium* TA1537
Cell count (overnight culture): 1.76 x 10^9 CFU/mL

Concentration: (µg/plate)		Revertant colony number -S9	Revertant colony number +S9
		10 P,R	9 P,R
		10 P,R	8 P,R
		10 P,R	11 P,R
	Mean	**10.0**	**9.3**
	SD	**0.00**	**1.53**
	MF	**1.07**	**1.08**
		8	9
		11	9
		14	10
	Mean	**11.0**	**9.3**
	SD	**3.00**	**0.58**
	MF	**1.18**	**1.08**
		12	8
		10	9
		14	11
	Mean	**12.0**	**9.3**
	SD	**2.00**	**1.53**
	MF	**1.29**	**1.08**
		10	8
		13	8
		13	11
	Mean	**12.0**	**9.0**
	SD	**1.73**	**1.73**
	MF	**1.29**	**1.04**
(b) (4)		11	7
		11	7
		11	9
	Mean	**11.0**	**7.7**
	SD	**0.00**	**1.15**
	MF	**1.18**	**0.88**
		8	9
		9	10
		8	11
	Mean	**8.3**	**10.0**
	SD	**0.58**	**1.00**
	MF	**0.89**	**1.15**
		11	9
		9	8
		9	9
	Mean	**9.7**	**8.7**
	SD	**1.15**	**0.58**
	MF	**1.04**	**1.00**
		8	7
		9	9
		10	10
	Mean	**9.0**	**8.7**
	SD	**1.00**	**1.53**
	MF	**0.96**	**1.00**

Concentration: (µg/plate)		Revertant colony number -S9	Revertant colony number +S9
Untreated control		9	9
		10	8
		10	8
	Mean	**9.7**	**8.3**
	SD	**0.58**	**0.58**
	MF	**1.04**	**0.96**
DMSO control*		7	7
		9	9
		11	10
	Mean	**9.0**	**8.7**
	SD	**2.00**	**1.53**
	MF	**0.96**	**1.00**
Distilled water		8	8
100 µL control**		10	8
		10	10
	Mean	**9.3**	**8.7**
	SD	**1.15**	**1.15**
	MF	**1.00**	**1.00**
Positive control		392	**2AA** 221
9AA		408	**(2 µg)** 208
(50 µg)		412	219
	Mean	**404.0**	**216.0**
	SD	**10.58**	**7.00**
	MF	**44.89**	**24.92**

P: Precipitate
R: Reduced background lawn development
MF: Mutation factor
SD: Standard deviation
+S9: with S9 mix
-S9: without S9 mix

$$\text{Mutation factor} = \frac{\text{mean revertants (test item)}}{\text{mean revertants (solvent control)}}$$

*DMSO control was used because of 9AA and 2AA

A P P E N D I C E S

Appendix 1
Copy of the Certificate of Analysis

CJ Research Institute of Biotechnology

55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, 16495, Korea, CJ BLOSSOM PARK
www.cj.co.kr
TEL : 031) 8099-2450 FAX : 031) 8099-2918

Certificate of analysis

Certificate No.	2021-PR-213	Receipt No.	2021-AN-178
Client		Date of Receipt	2021-10-27
Client Name		Date of Test	2021-10-28
Client Tel		Use of Report	Reference test
Client Address			

Test Sample	Tryptophan (TRP Pro)	
Manuf. Date	2021.10.05	
Lot. No	(b) (4)	
Quantity (kg)	-	
Test Item(s)	Test Result	Test method used
L-Tryptophan (dry basis)	(b) (4)	HPLC
Loss on drying		AOAC 934.01
* Information		

* Temperature : (20~28) ℃, Relative Humidity : (30~60) %
* The results shown in this test report refer only to the sample tested unless otherwise stated.
The Test Report cannot be reproduced, except in full.

(b)(6)

November 3, 2021

CJ Research Institute of Biotechnology

(b) (4)

Appendix 2
Historical Control Data
(Period of 2015-2020)

Untreated control data

	without metabolic activation (-S9 Mix)					with metabolic activation (+S9 Mix)				
	(b) (4)				E. coli	(b) (4)				E. coli
Mean	20.9	98.3	13.2	8.8	40.6	25.6	104.6	12.3	9.9	44.1
St. dev.	4.4	12.7	3.5	3.2	9.4	5.8	13.2	3.2	3.6	9.4
Range	11-50	67-152	1-33	2-26	14-77	13-54	67-152	3-39	1-29	16-89
n	1296	1297	1302	1314	1302	1311	1314	1314	1323	1299

DMSO control data

	without metabolic activation (-S9 Mix)					with metabolic activation (+S9 Mix)				
	(b) (4)				E. coli	(b) (4)				E. coli
Mean	20.5	95.4	13.0	8.4	39.6	24.9	101.0	11.8	9.4	43.0
St. dev.	4.2	12.1	3.5	3.1	9.7	5.4	13.5	3.1	3.5	9.5
Range	7-41	60-145	3-34	1-27	12-75	11-50	53-165	2-33	1-29	9-76
n	1428	1419	1425	1449	1425	1443	1443	1449	1455	1431

Distilled water control data

	without metabolic activation (-S9 Mix)					with metabolic activation (+S9 Mix)				
	(b) (4)				E. coli	(b) (4)				E. coli
Mean	21.5	97.5	13.2	9.3	41.5	25.9	103.1	12.1	10.4	44.6
St. dev.	4.4	12.5	3.3	3.4	9.1	5.6	13.6	3.1	3.7	9.0
Range	13-37	58-150	2-32	3-20	17-72	15-45	59-164	3-34	3-24	13-76
n	288	1332	1332	303	1341	291	1314	1326	300	1320

DMF control data

	without metabolic activation (-S9 Mix)					with metabolic activation (+S9 Mix)				
	(b) (4)				E. coli	TA98	TA100	TA1535	TA1537	E. coli
Mean					42.0	23.8	96.2	11.9	10.5	43.3
St. dev.	3.9	13.3	3.1	3.4	10.8	5.5	13.2	3.0	3.6	10.9
Range	11-33	57-121	6-24	2-18	16-70	11-37	68-143	3-21	3-19	18-72
n	114	114	114	117	111	114	114	114	114	111

Acetone control data

	without metabolic activation (-S9 Mix)					with metabolic activation (+S9 Mix)				
	(b) (4)				E. coli	(b) (4)				E. coli
Mean	20.9	97.1	12.9	8.2	40.1	25.5	102.2	11.5	9.1	44.1
St. dev.	4.3	10.0	3.6	2.8	8.5	5.6	11.3	3.0	3.2	8.7
Range	11-35	63-126	6-32	2-17	21-63	16-44	66-132	4-19	1-19	20-70
n	219	222	222	225	219	219	222	225	225	219

Positive reference control data

	without metabolic activation (-S9 Mix)					with metabolic activation (+S9 Mix)				
	(b) (4)				E. coli	(b) (4)				E. coli
Mean	395.9	1130.9	1138.8	413.3	1020.6	2391.6	2408.0	219.0	214.0	239.5
St. dev.	99.4	82.5	102.0	34.0	114.4	146.2	115.7	32.1	22.3	35.6
Range	182-2336	536-1480	568-2004	208-629	488-2496	312-2736	1116-3104	101-418	147-424	127-384
n	1296	1296	1302	1314	1305	1311	1317	1317	1323	1299

TA98: *Salmonella typhimurium* (b) (4): *Salmonella typhimurium* (b) (4): *Salmonella typhimurium* (b) (4): *Salmonella typhimurium* (b) (4) E. coli: *Escherichia coli* WP2 *uvrA;* n: number of cases

Appendix 2 (continued)
Historical Control Data
(2019)

Untreated control data		
	without metabolic activation (-S9 Mix)	with metabolic activation (+S9 Mix)
	Salmonella typhimurium (b) (4)	
Mean	290.9	313.7
St. dev.	12.8	24.8
Range	264-326	264-392
n	51	51

DMSO control data		
	without metabolic activation (-S9 Mix)	with metabolic activation (+S9 Mix)
	Salmonella typhimurium (b) (4)	
Mean	294.5	310.3
St. dev.	12.9	18.5
Range	276-332	285-384
n	51	51

Distilled water control data		
	without metabolic activation (-S9 Mix)	with metabolic activation (+S9 Mix)
	Salmonella typhimurium (b) (4)	
Mean	294.8	312.1
St. dev.	13.4	24.8
Range	256-331	242-384
n	51	48

Positive reference control data		
	without metabolic activation (-S9 Mix)	with metabolic activation (+S9 Mix)
	Salmonella typhimurium (b) (4)	
Mean	832.4	899.4
St. dev.	222.3	132.9
Range	566-1536	584-1216
n	51	51

Appendix 3
Copy of the GLP Certificate

(b) (4), (b)(6)



GOOD LABORATORY PRACTICE (GLP)
CERTIFICATE

It is hereby certified that the test facility

(b) (4)



is able to carry out

physico-chemical testing, toxicity studies, mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, analytical and clinical chemistry, pathology studies, preparation of microscopic tissue sections, reproduction toxicology, in vitro studies, inhalation toxicology, and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **07-11 May 2018.**

This certificate is valid till 11th of August, 2022.

(b)(6)



Note: Translation of the text of the certificate in the header: ("Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet") - ("National Institute of Pharmacy and Nutrition"); ("Hatósági Ellenőrzési Főosztály") - ("Inspectorate Division") and at the signature: ("Digitálisan aláírta") - ("Digitally signed"); ("Dátum") - ("Date").

Appendix 3 (continued)
Copy of the GLP Certificate



GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility



is able to carry out

physico-chemical testing, toxicity studies, mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, residue studies, analytical and clinical chemistry, pathology studies, preparation of microscopic tissue sections, reproduction toxicology, in vitro studies, inhalation toxicology, and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **09-11 May 2022.**

This certificate is valid till 12th of May, 2023.



Note: Translation of the text of the certificate in the header: ("Országos Gyógyszerészeti és Élelmezésegészségügyi Intézet") - ("National Institute of Pharmacy and Nutrition"); ("Hatósági Ellenőrzési Főosztály") - (Inspectorate Division); and at the signature: ("Digitálisan aláírta") - (Digitally signed); ("Dátum") - ("Date").

Appendix 9 Attachments 1 and 4 withheld entirely under Exemption (b)(4)

Test Report

No: 2021-MASS-09-17-21

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 9, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	[redacted]	⑥Analysis Period	August 10-August 12, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA. 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4)

Test Report

No: 2021-MASS-09-17-22

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 9, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	A-2	⑥ Analysis Period	August 10-August 12, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4)

Test Report

No: 2021-MASS-09-17-23

1. Client

① Name	(b) (4)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 9, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	A-3	⑥Analysis Period	August 10-August 12, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4)

Test Report

No: 2021-MASS-09-17-29

1. Client

① Name	(b) (4)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 17, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	β-1	⑥ Analysis Period	August 18-August 19, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA. 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4)

Test Report

No: 2021-MASS-09-17-30

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 17, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	B-2	⑥Analysis Period	August 18-August 19, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4)

Test Report

No: 2021-MASS-09-17-31

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 17, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	B-3	⑥Analysis Period	August 18-August 19, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4), (b) (6)

(b) (4)

Test Report

No: 2021-MASS-09-17-32

1. Client

① Name	(b) (6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 17, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	B-4	⑥Analysis Period	August 18-August 19, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4), (b) (6)

(b) (4)

Test Report

No: 2021-MASS-09-17-33

1. Client

① Name	(b) (6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 17, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	B-5	⑥Analysis Period	August 18-August 19, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4), (b) (6)

(b) (4)

Test Report

No: 2021-MASS-09-17-34

1. Client

① Name	(b) (6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 17, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	C-1	⑥Analysis Period	August 18-August 19, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4), (b) (6)

(b) (4)

Test Report

No: 2021-MASS-09-17-35

1. Client

① Name	(b) (6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 17, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	C-2	⑥Analysis Period	August 18-August 19, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4), (b)(6)

(b) (4)

Test Report

No: 2021-MASS-09-17-36

1. Client

① Name	(b) (6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 17, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	C-3	⑥Analysis Period	August 18-August 19, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4), (b)(6)

(b) (4)

Test Report

No: 2021-MASS-09-17-37

1. Client

① Name	(b) (6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 17, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	C-4	⑥Analysis Period	August 18-August 19, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4), (b) (6)

(b) (4)

Test Report

No: 2021-MASS-10-29-1

1. Client

① Name	(b) (4)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8090-1515

2. Sample Description

① Receipt No	2021-MS-C-00471	② Receipt Date	September 27, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	D-1	⑥Analysis Period	October 1-October 5, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

October 29. 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4), (b)(6)

Test Report

No: 2021-MASS-10-29-2

1. Client

① Name	(b) (6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00471	② Receipt Date	September 27, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	D-2	⑥Analysis Period	October 1-October 5, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
iMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client
and it is the decision of the client naming the presented sample.

October 29. 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4), (b)(6)

Test Report

No: 2021-MASS-10-29-3

1. Client

① Name	(b) (6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No	2021-MS-C-00471	② Receipt Date	September 27, 2021
③ Sample Type	Powder	④ Quantity	1
⑤ Sample Name	D-3	⑥Analysis Period	October 1-October 5, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indolylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

October 29. 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4), (b)(6)

[redacted]

Test Report

No: 2021-MASS-09-17-24

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 9, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	LATE FINISHER SWINE DIET (US)	⑥Analysis Period	August 10-August 12, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4), (b)(6)

(b) (4)

Test Report

No: 2021-MASS-09-17-25

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	August 9, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	FINISHER SWINE DIET (US)	⑥Analysis Period	August 10-August 12, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indolylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4), (b)(6)

(b) (4)

Test Report

No: 2021-MASS-09-17-6

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	June 17, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	Feed Finishing Pig (KR)	⑥Analysis Period	June 17, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4), (b)(6)

(b) (4)

Test Report

No: 2021-MASS-09-17-7

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	June 17, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	Finishing Pig 3 (KR)	⑥Analysis Period	June 17, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4), (b) (6)

(b) (4)

Test Report

No: 2021-MASS-09-17-11

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	June 17, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	Finishing Pig 2 (KR)	⑥Analysis Period	June 17, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4), (b)(6)

(b) (4)

Test Report

No: 2021-MASS-09-17-12

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	June 17, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	Finishing Pig 1 (KR)	⑥Analysis Period	June 17, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4), (b)(6)

(b) (4)

Test Report

No: 2021-MASS-09-17-10

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	June 17, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	Weaning Pig (KR)	⑥Analysis Period	June 17, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4), (b)(6)

(b) (4)

Test Report

No: 2021-MASS-09-17-8

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	June 17, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	Feed Weaning Pig (KR)	⑥Analysis Period	June 17, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4), (b)(6)

(b) (4)

Test Report

No: 2021-MASS-09-17-9

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	June 17, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	Growing Pig (KR)	⑥Analysis Period	June 17, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4), (b)(6)

(b) (4)

Test Report

No: 2021-MASS-09-17-13

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	June 17, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	Farrowing Saw (KR)	⑥Analysis Period	June 17, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PiC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1 2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2 3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4), (b)(6)

(b) (4)

Test Report

No: 2021-MASS-09-17-14

1. Client

① Name	(b)(6)	② Company	CJ CheilJedang
③ Address	55, Gwanggyo-ro 42beon-gil, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea	④ Telephone	+82-31-8099-1515

2. Sample Description

① Receipt No.	2021-MS-C-00361	② Receipt Date	June 17, 2021
③ Sample Type	Granule	④ Quantity	1
⑤ Sample Name	Farrowing Saw (KR)	⑥Analysis Period	June 17, 2021

Test Results

	Method	Unit	Test Result	LOD	LOQ
EBT	LC-MS/MS	mg/kg	(b) (4)		
HTP	LC-MS/MS	mg/kg			
IMT	LC-MS/MS	mg/kg			
MTCA	LC-MS/MS	mg/kg			
PIC	LC-MS/MS	mg/kg			

EBT: 1,1'-ethylidenebistryptophan
HTP: 5-hydroxytryptophan
IMT: 2-(3-indoylmethyl)-L-tryptophan
MTCA: 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid
PIC: 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid

This test report shall be used within the purpose of its defined usage.
The results have been made for the sample supplied by the client,
and it is the decision of the client naming the presented sample.

September 17, 2021

This is to inform the results of laboratory analysis according to the regulations for the testing and analysis at (b) (4)

(b) (4)

(b) (4), (b)(6)

(b) (4)

Biogenic amines in fermentation broth

CJ CheilJedang analyzed the biogenic amines in fermentation broth to 3rd party laboratory, (b) (4) Sample information and analytical result of each samples are provided in Table 1 and 2, respectively.

Table 1. Sample information

Sample name	Sample description	As provided in
(b) (4)	Fermentation broth of ATCC (b) (4) (wild-type strain)	Appendix 2_Pre-fermentation Information (C. Spill-over analysis, Table C.2.2)
	Fermentation broth of ATCC (wild-type strain)	
	Fermentation broth of ATCC (wild-type strain)	
	Fermentation broth of KCCM 80346 (production strain)	
	Fermentation broth of KCCM 80346 (production strain)	
	Fermentation broth of KCCM 80346 (production strain)	

The level of biogenic amines (Table 2) in the *C. glutamicum* KCCM 80346 fermentation broth is almost same with *C. glutamicum* ATCC (b) (4) Therefore, it can be concluded that there is no concern about spill-over effect by strain development.

Table 2. Analytical result (Appendix 10_Attachment 1_Certificate of analysis_fermentation broth)

Sample name	Cadaverine (mg/l)	Histamine (mg/l)	Phenylethyl-amine (mg/l)	Putrescine (mg/l)	Tryptamine (mg/l)	Tyramine (mg/l)
(b) (4)						

Table 3. Spike sample information

Sample name	Sample Description
(b) (4)	

Table 4. Spike test result (Appendix 10_Attachment 1_Certificate of analysis_fermentation broth)

(a) Fermentation broth (b) (4)

Biogenic amine	Spiking concentration (ng/ml)	Final concentration (ng/ml)	Recovery (%)
Cadaverine	(b) (4)		
Histamine			
Phenylethylamine			
Putrescine			
Tryptamine			
Tyramine			

(b) Fermentation broth (b) (4)

Biogenic amine	Spiking concentration (ng/ml)	Final concentration (ng/ml)	Recovery (%)
Cadaverine	(b) (4)		
Histamine			
Phenylethylamine			
Putrescine			

Appendix 10. Biogenic amines in fermentation broth (CONFIDENTIAL)

Biogenic amine	Spiking concentration (ng/ml)	Final concentration (ng/ml)	Recovery (%)
	(b) (4)		
Tryptamine			
Tyramine			

[Appendix 1] Summary of the analytical method

(b) (4)

B. Analytical condition

(a) LC condition

System	(b) (4)
Column	
Mobile phase	
Gradient mode	
Column temperature	
Sample temperature	
Injection volume	

(b) MS/MS condition

System	(b) (4)
Ion Source Type	
Positive Ion (V)	
Ion Transfer Tube Temp	
Vaporizer Temp (°C)	
Polarity	
MRM condition	

	(b) (4)
Putrescine	
Putrescine	
Putrescine	
Cadaverine	
Cadaverine	
Cadaverine	
Histamine	
Histamine	
Histamine	
Tyramine	
Tyramine	
Tyramine	

C. Results

a) Chromatogram

RT 7.20 - 10.67

(b) (4)

2) Calibration curve

The concentration of biogenic amines were calculated based on the equation from the calibration curve.

(b) (4)

(b) (4)

3) LOD/LOQ calculation

(b) (4)

The limit of quantitation can also be calculated:

LOQ= 10 × sd (standard deviation)

Table S1. LOD and LOQ of biogenic amines

	Biogenic amines (ng/mL)					
	Tryptamine	**Phenylethyl-amine**	**Putrescine**	**Cadaverine**	**Histamine**	**Tyramine**
1	(b) (4)					
2						
3						
4						
5						
6						
7						
Standard deviation						
LOD						
LOQ						

CJ CHEILJEDANG BLOSSOM PARK

55, Gwanggyo-ro 42beon-gil, Yeongtong-gu,

Suwon-si, Gyeonggi-do, Republic of Korea

Our reference:	EUKR01-00021907 / (b) (4)		
Sample Description:	TRP Pro		
Lot NO.	(b) (4)		
Reception Date:	09-Nov-2022		
Test Purpose	Voluntary testing		
Product Type	Granule	Sample Weight	100g

Test Result(s):

	Results	Unit	Guideline
☆ DJ700 Biogenic Amines (dansyl) Method: Czech J. Food Sci. Vol.21, LC-UV/DAD	(b) (4)		
2-Phenylethylamine		mg/kg	
Cadaverine		mg/kg	
Histamine		mg/kg	
Putrescine		mg/kg	
Spermidine		mg/kg	
Spermine		mg/kg	
Tryptamine		mg/kg	
Tyramine		mg/kg	

SIGNATURE (b)(6)

(b) (4)

END OF REPORT

(b) (4)

Received on	14-11-2022	**Report code**	AR-22-DJ-094755-01
Analysis start	14-11-2022	**EOL batch**	
Analysis completed	20-11-2022	**Batch code**	(b) (4)
Report complete	20-11-2022	**Sample code**	487-2022-11140134
Sample description §	TRP Pro		
Sample marking §	(b) (4)		
Sample comment §	- TRP Pro		

Test	Parameter	Result	Unit	U(%)	Est. value
DJ700	*Czech J. Food Sci. Vol.21 / LC-UV/DAD*	(b) (4)			
	# 2-Phenylethylamine				
	# Cadaverine			14	
	Histamine				
	# Putrescine				
	# Spermidine			14	
	# Spermine				
	# Tryptamine			20	
	# Tyramine			8	

<L.Q. / <LOQ	:Below limit of quantification	ND / N.D.	:Not detected	<	:Less than/below
<L.D. / <LOD	:Below limit of detection	*x dupl*	*:x determination*	>	:Greater than/above

#: Not accredited

(b)(6)

(b) (4), (b) (6)

(b) (4)

CJ CHEILJEDANG BLOSSOM PARK

55, Gwanggyo-ro 42beon-gil, Yeongtong-gu,

Suwon-si, Gyeonggi-do, Republic of Korea

Our reference:	EUKR01-00021907 / (b) (4)		
Sample Description:	TRP Pro		
Lot NO.	(b) (4)		
Reception Date:	09-Nov-2022		
Test Purpose	Voluntary testing		
Product Type	Granule	Sample Weight	100g

Test Result(s):

	Results	Unit	Guideline
☆ DJ700 Biogenic Amines (dansyl) Method: Czech J. Food Sci. Vol.21, LC-UV/DAD	(b) (4)		
2-Phenylethylamine		mg/kg	
Cadaverine		mg/kg	
Histamine		mg/kg	
Putrescine		mg/kg	
Spermidine		mg/kg	
Spermine		mg/kg	
Tryptamine		mg/kg	
Tyramine		mg/kg	

SIGNATURE (b)(6)

(b) (4)

(b) (4), (b) (6)

(b) (4)

Att: Result

Received on	14-11-2022	**Report code**	AR-22-DJ-094756-01
Analysis start	14-11-2022	**EOL batch**	
Analysis completed	20-11-2022	**Batch code**	EUDAKG-00435717
Report complete	20-11-2022	**Sample code**	487-2022-11140135
Sample description §	TRP Pro		
Sample marking §	(b) (4)		
Sample comment §	- TRP Pro		

Test	Parameter	Result	Unit	U(%)	Est. value
DJ700	*Czech J. Food Sci. Vol.21 / LC-UV/DAD*	(b) (4)			
	# 2-Phenylethylamine				
	# Cadaverine			14	
	Histamine			16	
	# Putrescine			26	
	# Spermidine			14	
	# Spermine				
	# Tryptamine			20	
	# Tyramine			8	

(b) (4), (b)(6)

(b) (4)

CJ CHEILJEDANG BLOSSOM PARK

55, Gwanggyo-ro 42beon-gil, Yeongtong-gu,

Suwon-si, Gyeonggi-do, Republic of Korea

Our reference:	EUKR01-00021907 / (b) (4)		
Sample Description:	TRP Pro		
Lot NO.	(b) (4)		
Reception Date:	09-Nov-2022		
Test Purpose	Voluntary testing		
Product Type	Granule	Sample Weight	100g

Test Result(s):

	Results	Unit	Guideline
☆ DJ700 Biogenic Amines (dansyl) Method: Czech J. Food Sci. Vol.21, LC-UV/DAD	(b) (4)		
2-Phenylethylamine		mg/kg	
Cadaverine		mg/kg	
Histamine		mg/kg	
Putrescine		mg/kg	
Spermidine		mg/kg	
Spermine		mg/kg	
Tryptamine		mg/kg	
Tyramine		mg/kg	

SIGNATURE (b)(6)

(b) (4)

END OF REPORT

(b) (4)

(b) (4)

Received on	14-11-2022	**Report code**	AR-22-DJ-094757-01
Analysis start	14-11-2022	**EOL batch**	
Analysis completed	20-11-2022	**Batch code**	EUDAKG-00435717
Report complete	20-11-2022	**Sample code**	487-2022-11140136

Sample description §	TRP Pro
Sample marking §	(b) (4)
Sample comment §	- TRP Pro

Test	Parameter	Result	Unit	U(%)	Est. value
DJ700	*Czech J. Food Sci. Vol.21 / LC-UV/DAD*	(b) (4)			
	# 2-Phenylethylamine				
	# Cadaverine			14	
	Histamine			16	
	# Putrescine			26	
	# Spermidine			14	
	# Spermine				
	# Tryptamine			20	
	# Tyramine			8	

(b) (4), (b)(6)

Liquid Chromatographic Determination of Biogenic Amines in a Meat Product during Fermentation and Long-term Storage

Dana SMĚLÁ[1], Pavla PECHOVÁ[2], Tomáš KOMPRDA[2], Bořivoj KLEJDUS[1] and Vlastimil KUBÁŇ[1]

[1]Department of Chemistry and Biochemistry and [2]Department of Food Technology, Mendel University of Agriculture and Forestry in Brno, Brno, Czech Republic

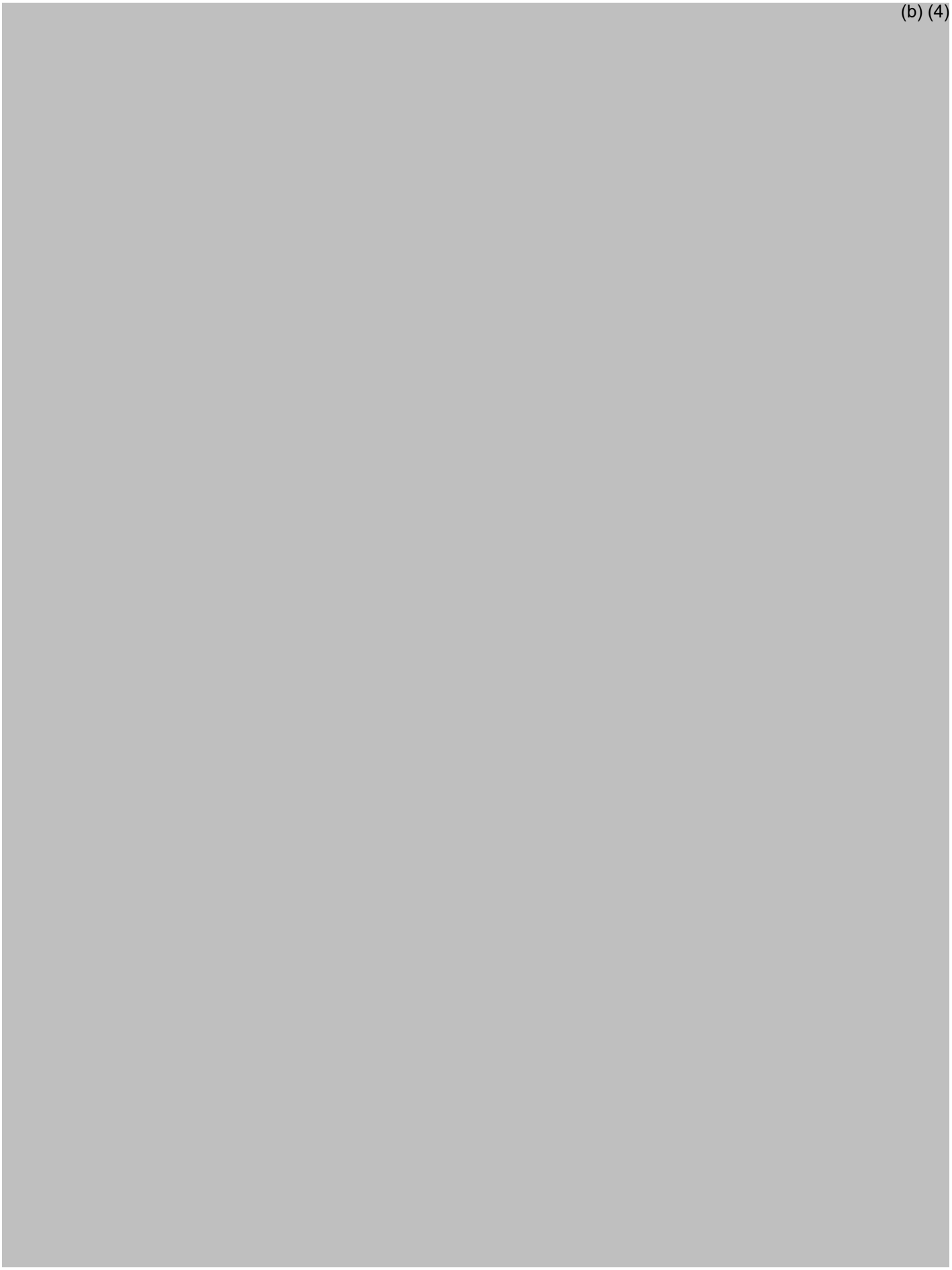
Abstract

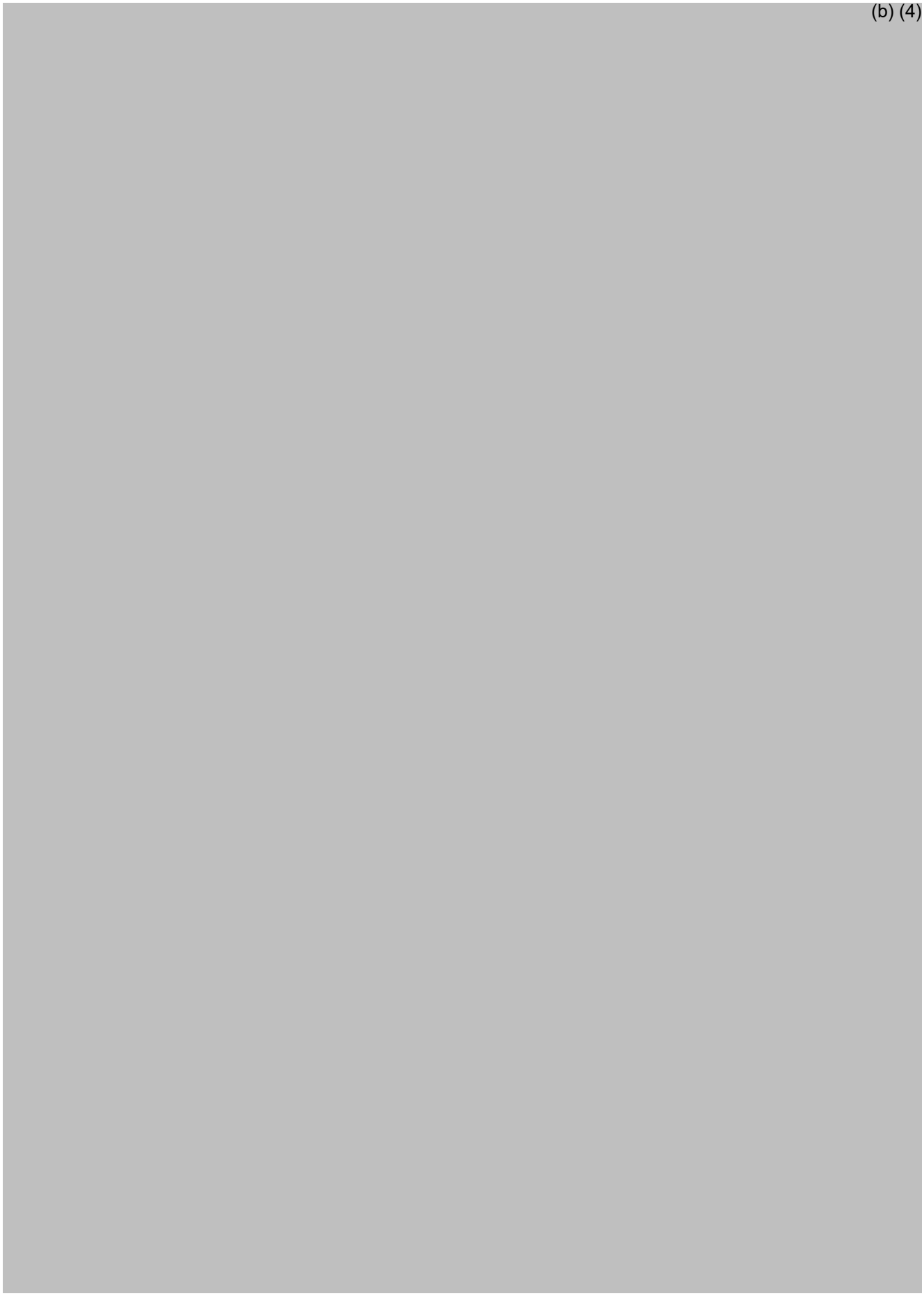
Směl á D., Pechová P., Komprda T., Klejdus B., Kubáň V. (2003): **Liquid chromatographic determination of biogenic amines in a meat product during fermentation and long-term storage.** Czech J. Food Sci., **21**: 167–175.

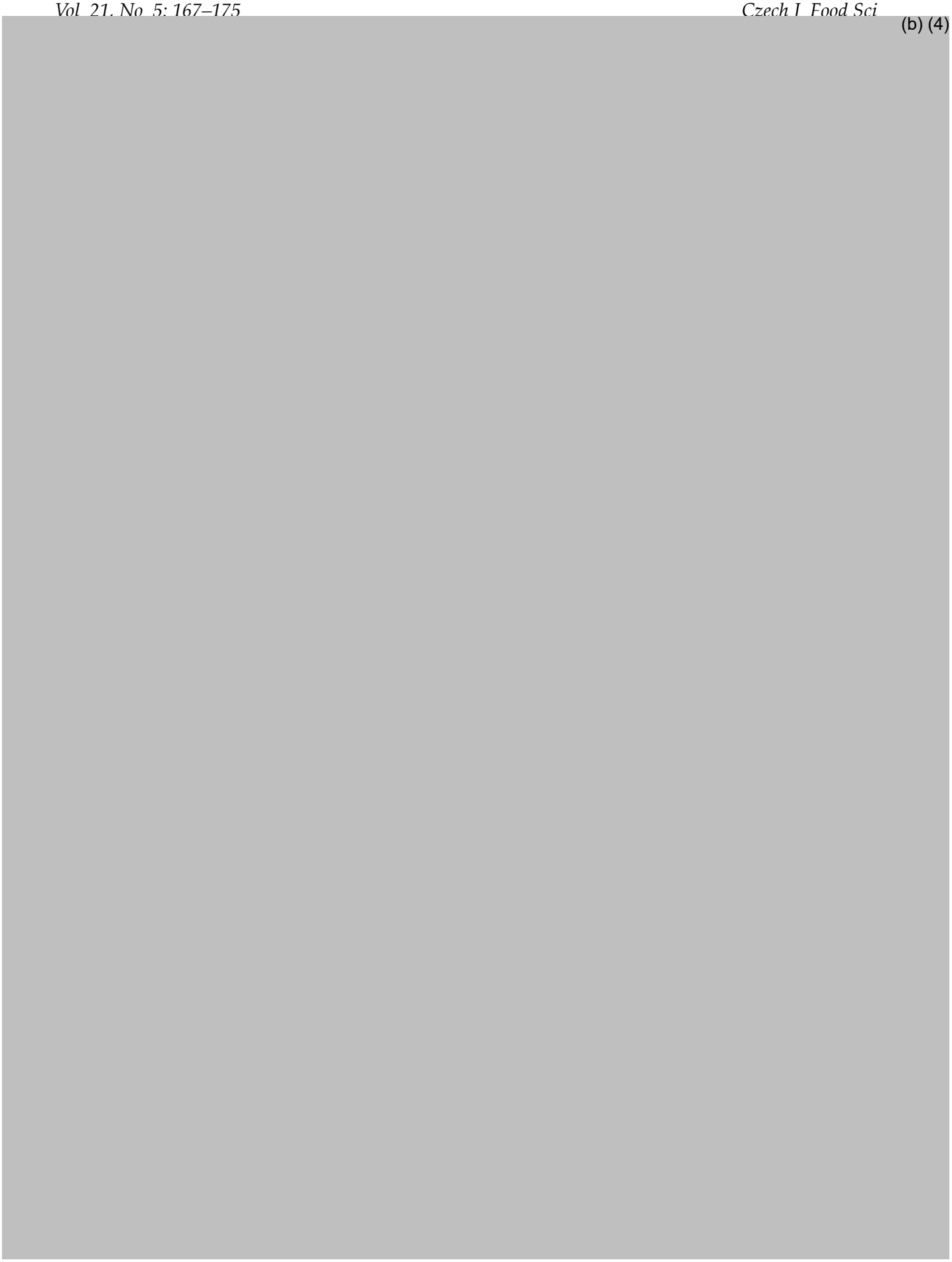
Liquid chromatographic procedures employing two derivatisation reagents, dansylchloride and *o*-phthaldialdehyde (OPA), were compared and applied for the determination of biogenic amines in meat products during fermentation and long-term storage. Both methods give similar results in terms of the detection limits, repeatability, recovery, and accuracy. Secondary amines (spermine and spermidine) do not react with *o*-phthaldialdehyde thus only their LC determination after derivatisation with dansylchloride is possible. Their contents during fermentation and/or long-term storage are nearly constant or slightly decrease, thus their determination in both cases is not necessary. LC procedure employing OPA derivatisation is faster, much simpler in terms of the pre-treatment of samples, and it can be fully automated using an intelligent auto sampler.

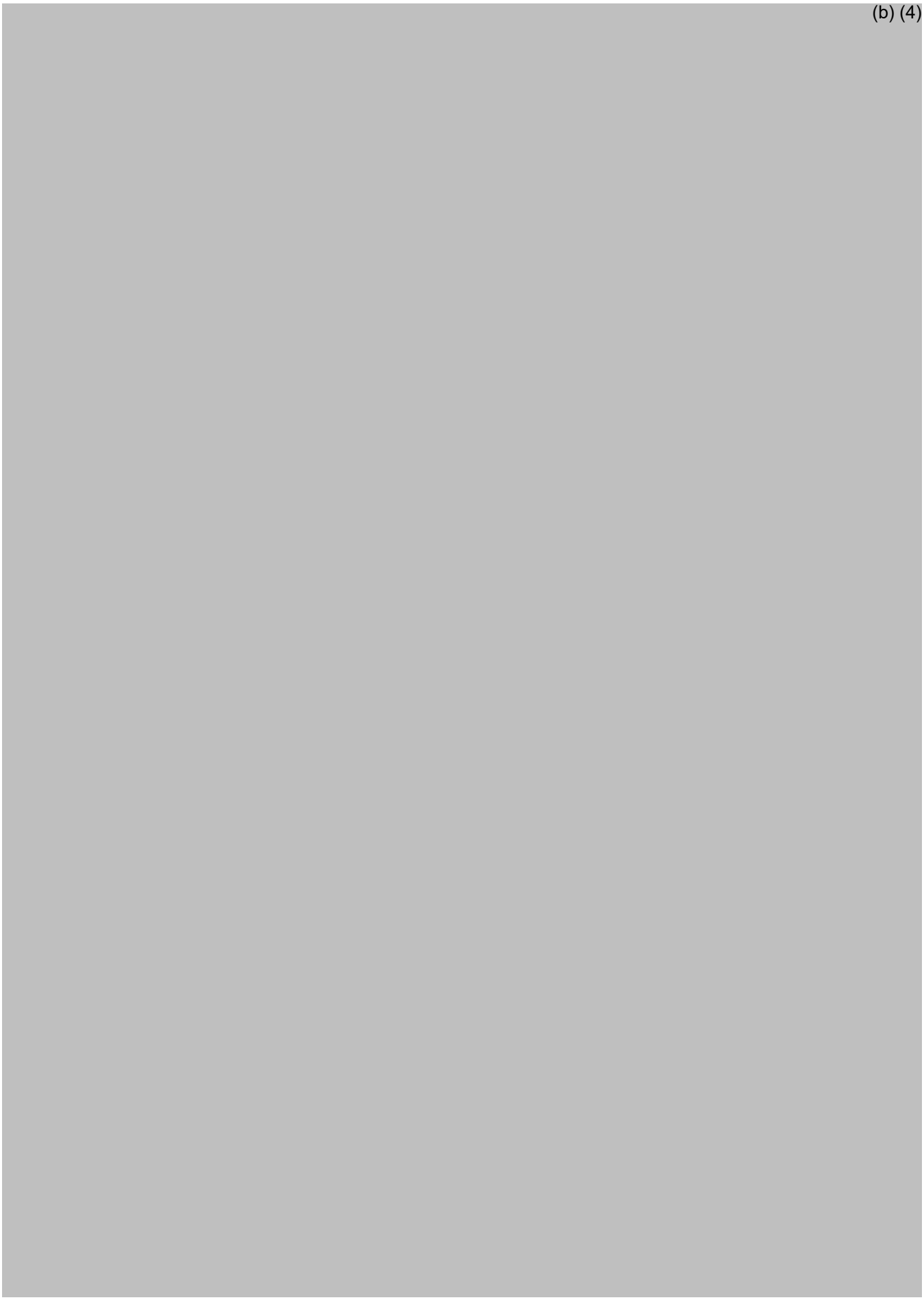
Keywords: biogenic amines; polyamines; HPLC determination; food; dry fermented sausage; ripening; storage

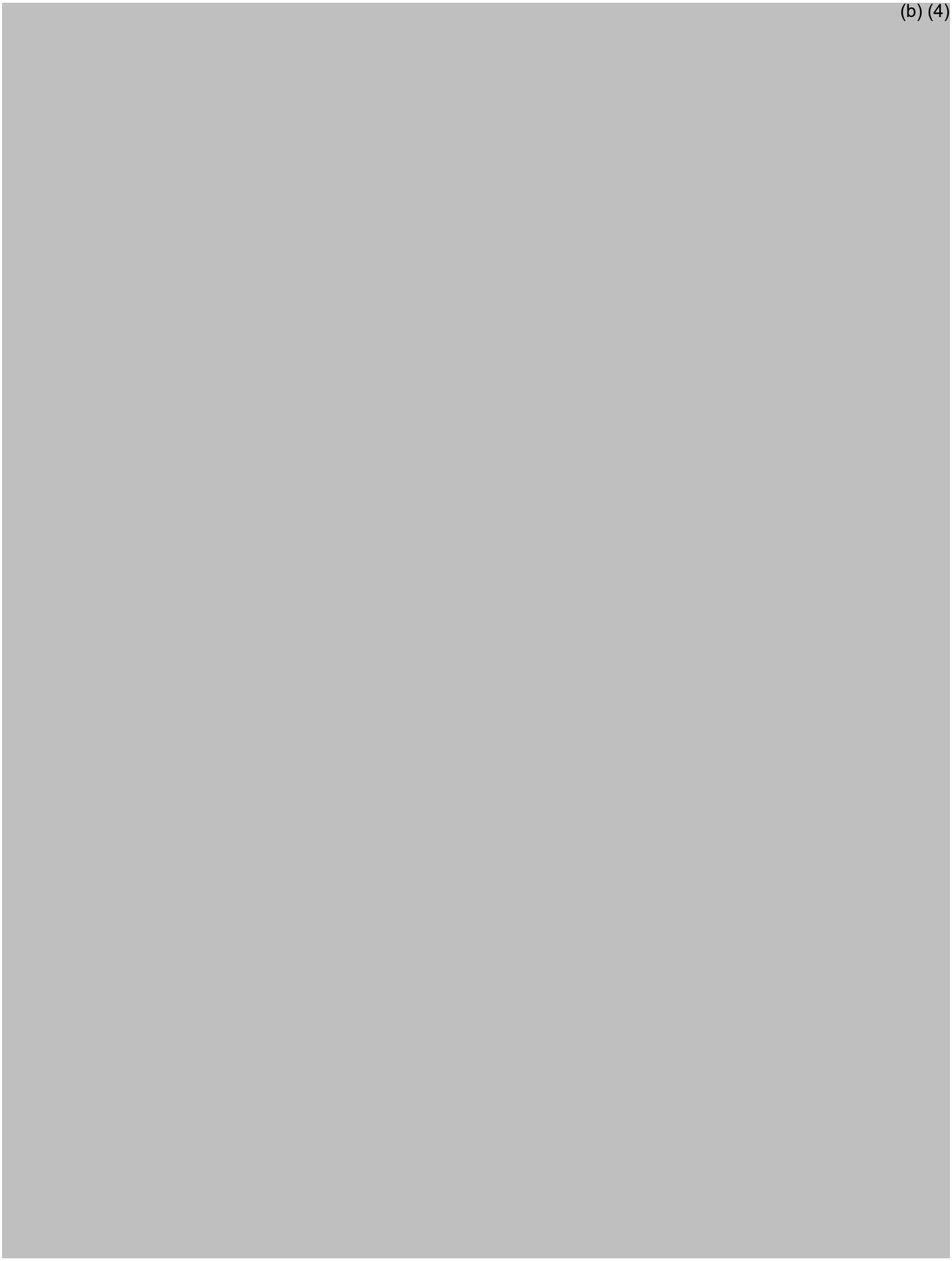
(b) (4)

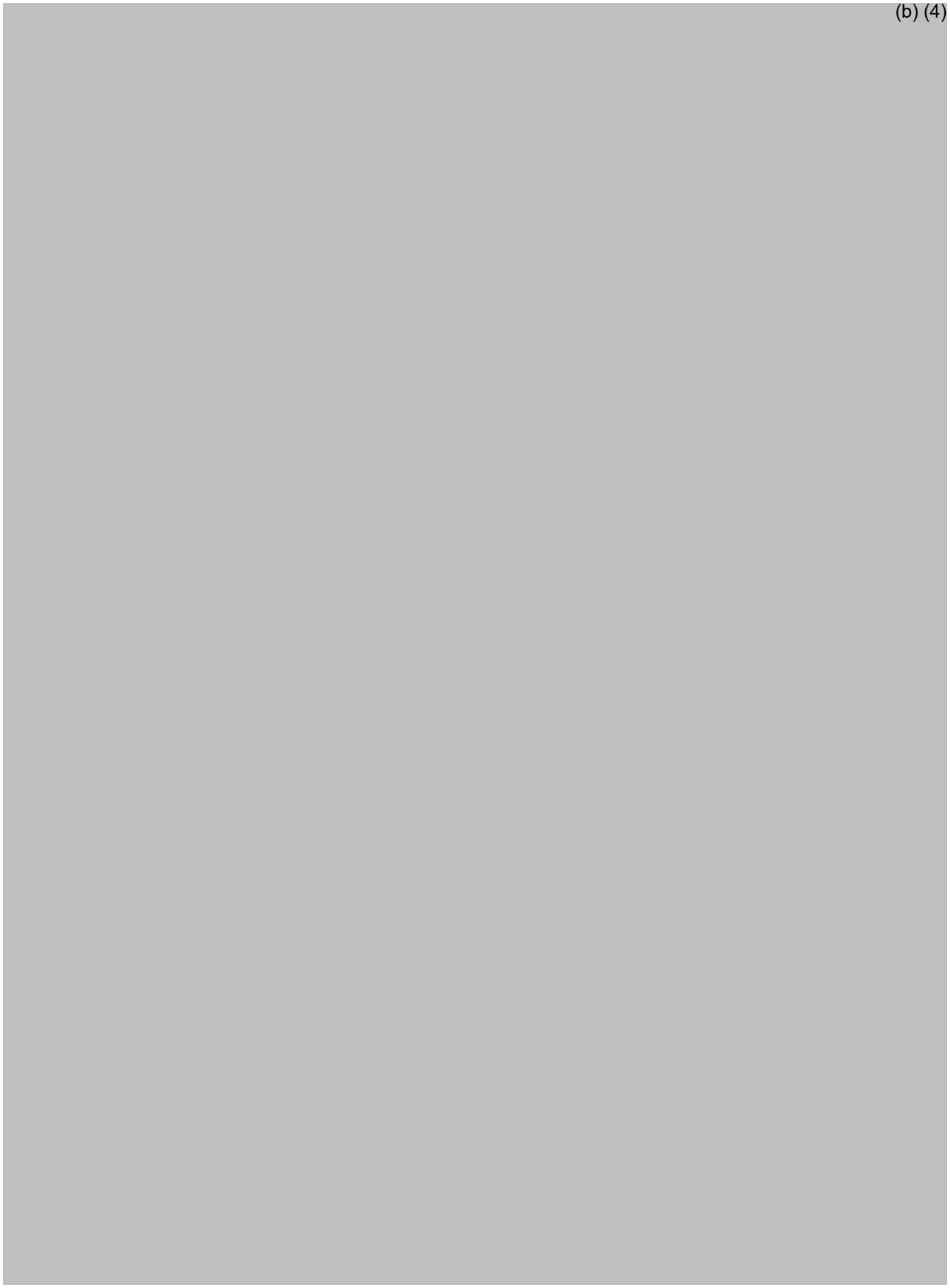

(b) (4)

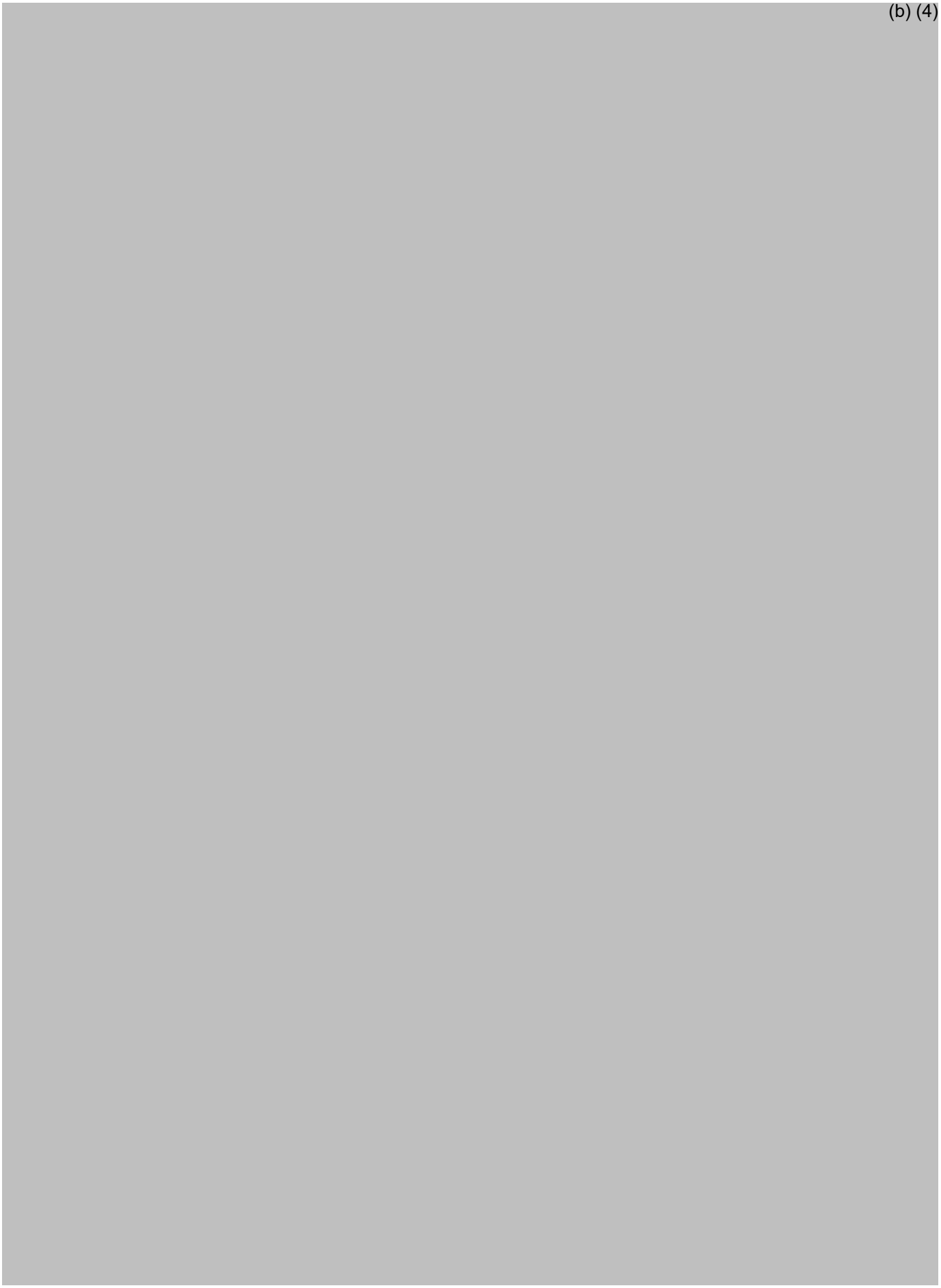

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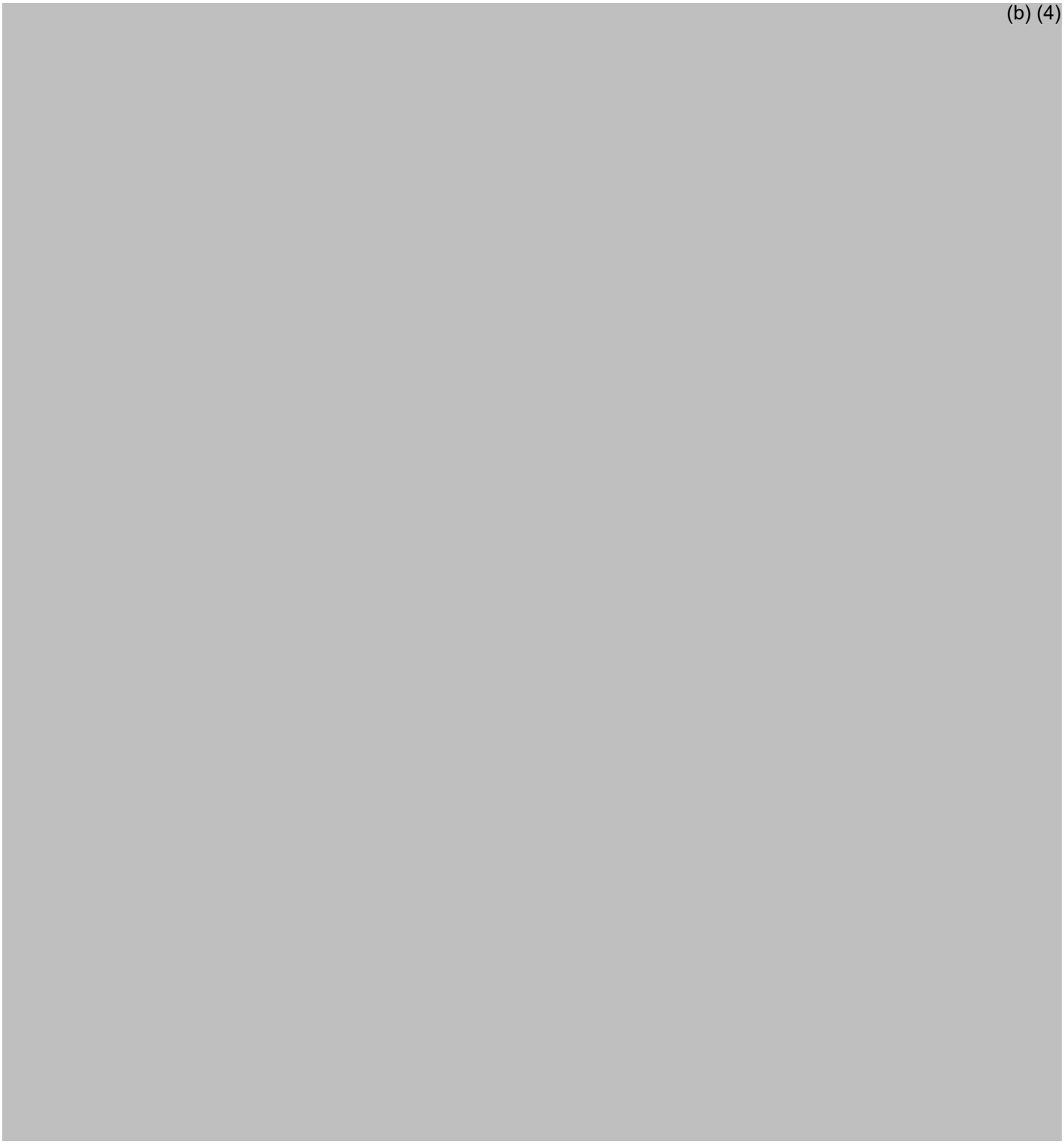

(b) (4)


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(b) (4)

ACCREDITATION

for testing

(b) (4)

Company (b) (4)

Scope of accreditation
- Testing, as specified in annex 1

Validity 08-07-2021 to 31-08-2025

Replaces document of 30-06-2020

Basis for accreditation **DS/EN ISO/IEC 17025:2017**

The laboratory complies with the requirements in DS/EN ISO/IEC 17025:2017 - General requirements for the competence of testing and calibration laboratories, together with the relevant provisions as an accredited body for the above mentioned scope of accreditation.

08-07-2021

(b) (4), (b)(6)

Testing

Accreditation for testing in compliance with requirements in DS/EN ISO/IEC 17025:2017.

(b) (4)

