

CONFIDENTIAL - CONTAINS PROPRIETARY STRUCTURES

Computational Toxicology Report on

- **Group A: Chemical A01 to A09**
- **Group B: Chemical B01**
- **Group C: Chemical C01 to C15**
- **Group D: Chemical D01 to D05**

DATE: {date}

FROM: FDA/CDER/OPS/ICSAS (HFD-901)

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REGULATORY NOTICE: The information in this report can not be used, and has not been approved for use, as the sole basis of any regulatory action or recommendation by FDA or CDER. The information in this report is intended for use as decision support in conjunction with other experimental/clinical data.

DISCLAIMER: MultiCASE *MC4PC*-based computational toxicology estimations are intended to be used as part of a weight of evidence approach for hazard and risk assessment that includes laboratory experimental data. Computational toxicology predictions are not intended as a substitute for appropriate animal or clinical studies.

NON-FDA and FDA CLIENT WARNINGS: The identity of proprietary compounds cannot be disclosed outside of the FDA, and care must be taken not to publicly disclose or share such information with non-FDA individuals or institutions. Proprietary compounds from non-FDA clients are represented by code numbers. FDA proprietary compounds are identified by the symbol \$\$\$.

Results obtained with certain *MC4PC* software modules should be regarded as preliminary and subject to change. The *MC4PC* rodent carcinogenicity modules are publically available through MultiCASE, Inc., and have been formally validated. Also validated and available are the *MC4PC* MRTD modules. In addition, FDA/CDER/OPS/ICSAS has conducted successful validation tests of the *MC4PC* teratogenicity, *Salmonella t.* mutagenicity, maximum tolerated dose, maximum recommended therapeutic dose, adverse liver, immunological, kidney and cardiological effect modules. Reports describing experimental materials, methods, and the results of these tests are being submitted for publication.

COMPOUND STRUCTURE(s): The test compound structures were provided by {name}.

DRUG CODE(s): The test compounds are Chemical A01 to 09, B01, C01 to C15, and D01 to 05. Their structures are presented in **Figures 1a to 1d**. The test compounds were divided into four groups based on their similar chemical structures. A total of seventeen (17) model compounds were identified as similar to compounds in each of the four groups. The structures for the model compounds are presented in **Figures 2a to 2d**.

COMPUTATIONAL TOXICOLOGY SOFTWARE: The *MC4PC* software programs were developed under a Cooperative Research and Development Agreement (CRADA) between FDA/CDER and MultiCASE, Inc. The software modules have been shown to have high coverage (>85%) for FDA-regulated substances (*i.e.*, food additives and pharmaceuticals). The predictive performance of the *MC4PC* software has been optimized by FDA/CDER to provide high specificity (>85%), high predictive value (>85%), and low false positive rates (<15%) for all of the toxicological and adverse effect endpoints; however, the sensitivity/false negative rate of the software is variable and dependent upon the size of training data sets in the individual toxicological endpoint database modules. The sensitivities for three *MC4PC* toxicological endpoints were: ~55% for rodent carcinogenicity; ~50% for mammalian teratogenicity; and ~60% for *Salmonella t.* mutagenicity. Therefore, positive (active) predictions reported below are regarded as reliable, but negative (inactive) predictions are less reliable and can only be regarded as failure to provide evidence for a positive prediction. The high precision of the predictions is dependent upon the use of human expert rules to evaluate the results of experimental data.

I. SUMMARY

A computational toxicology study was performed on forty-seven (47) compounds, including thirty (30) test compounds from {name}. The names and molecular structures of the structurally similar model pharmaceutical compounds were obtained from the Derwent World Drug Index (www.derwent.com) and are thereby non-proprietary data.

This computational toxicology report reflects the capabilities of the FDA/CDER Computational Toxicology and Toxicology Database programs as of the date of this report. MC4PC version 1.55 and MCASE version 3.55 were used for these evaluations.

Table 0 presents a summary of the predicted activities of 47 compounds at ten different endpoints: (1) carcinogenicity in rodents (rats and mice); (2) teratogenicity in mammals (rabbits, rats and mice); (3) mutagenicity in *Salmonella typhimurium*; (4) adverse liver side effects in adult humans; (5) adverse immunological side effects in adult humans; (6) adverse kidney side effects in adult humans; (7) adverse cardiological side effects in adult humans; (8) MTD in rats and mice; (9) human MRTD/NOEL; and (10) LD₅₀ in rats and mice. The MC4PC predictions in **Table 0** are the principle investigator's expert assessment of the MC4PC program's experimental data which may not be the same as the raw default, "non-expert" predictions obtained with the software.

The molecular composition of both test and model compounds were checked for their representation (coverage) among the molecular structures found in the control database (training set) of chemical substances. The incidence of unknown MC4PC fragments is summarized in **Table 0** and reported in detail in the description of the results for each individual endpoint analyzed and in **Tables 1 - 10** ("w" represents an unknown fragment). Substances are considered uncovered for MC4PC analyses if they contain more than one unknown fragment ("2w" or more) for more than 50% of the modules. The test and model compounds were adequately coverage for most of the endpoints in this study.

The results of this investigation for non-clinical endpoints showed that ten (10/47) compounds are predicted to be carcinogenic in rodents and eight (8/47) compounds are predicted to be possibly carcinogenic. Eight (8/47) compounds are predicted to be teratogenic in mammals and three (3/47) are predicted to be mutagenic in *Salmonella typhimurium*. Four compounds have been experimentally tested at one or more of these endpoints.

For clinical endpoints, the results showed that four (4/47) compounds are predicted to cause adverse liver side effects, five (5/47) compounds are predicted to cause adverse immunological effects in adult humans, four (4/47) compounds are predicted to cause adverse kidney effects, and two (2/47) are predicted to possibly cause these effects. Finally, eleven (11/47) compounds are predicted to cause adverse cardiological effects, and seven (7/47) compounds are predicted to possibly cause these effects. Three (3/47) of these compounds tested are also present in the training data set for all four clinical endpoints.

For MTD, the forty-seven (47) compounds are predicted to have a range of values from 0.67 to 1500 mg/kg-bw/day in rats, and 0.0020 to >5000 mg/kg-bw/day in mice. For MRTD, the forty-seven (47) compounds are predicted to have a range of values from 0.0030 to 70 mg/kg-bw/day, and a range of NOEL dose values from 0.00030 to 7.0 mg/kg-bw/day. For LD₅₀, forty-seven (47) compounds are predicted to have range of values from 560 to >5000 mg/kg-bw in rats, and from 7.4 to >5000 mg/kg-bw in mice. Three (3/47) compounds have been experimentally evaluated at one of more of the dose endpoints.

Table 0 also contains a column for the chemical similarity index (S.I.) and bioavailability (Bio.) for each compound. The S.I. is determined by the ISIS™/HOST software and bioavailability is determined by MC4PC. The latter is predicted using Lipinski's rule of five [Lipinski, C.A. *et al.* Experimental and computational approaches to estimate solubility and permeability in drug discovery and developmental settings. *Advanced Drug Deliv. Rev.* **23**:3-25, 1997] and is given the designation "LR+" (compound is predicted bioavailable) or "LR+?" (compound may not be bioavailable). The ISIS data demonstrated that the model compounds have structural similarity ranging from 35 to 95% to their corresponding test compound. The MC4PC data showed that forty-four (44/47) compounds are bioavailable according to Lipinski's rule of five.

Table 0: Summary of the Actual Experimental and MC4PC and MCASE Predicted Toxicological and Adverse Effect Activities and Doses of Forty-seven (47) Compounds

Chemical Name	Chemical S.I.	Bio.	Toxicological / Adverse Effect Activity						
			1	2	3	4	5	6	7
			<u>MC4PC</u> <u>Carc.</u>	<u>MC4PC</u> <u>Terat.</u>	<u>MC4PC</u> <u>Salm.</u>	<u>MC4PC</u> <u>Liver</u>	<u>MC4PC</u> <u>Imm.</u>	<u>MC4PC</u> <u>Kid.</u>	<u>MC4PC</u> <u>Card.</u>
TEST AND MODEL COMPOUNDS									
Group A									
001 Chemical A01	1.00	LR+?	+	-	-	-	-	-*	+?*
002 Chemical A02	-----	LR+	+	-	-	-	-	-*	+
003 Chemical A03	-----	LR+?	-	-	-	-	-	+	+
004 Chemical A04	-----	LR+?	-	-	-	-	-	-	+?
005 Chemical A05	-----	LR+	+	-	-	-	-	+	+
006 Chemical A06	-----	LR+	-	-	_*	_*	_*	_*	+
007 Chemical A07	-----	LR+	+	-	-	-	-	_*	+
008 Chemical A08	-----	LR+	+	-	_*	_*	_*	_*	+
009 Chemical A09	-----	LR+	+	-	-	-	-	_*	+
010 Chemical A101	0.95	LR+	+	-	-	-	-	+	+
011 Chemical A102	0.90	LR+	+	-	-	-	-	_*	+
012 Chemical A103	0.70	LR+	+	-	-	-	-	+	+
013 Chemical A104	0.70	LR+	+	-	-	-	+	+	+
Group B									
014 Chemical B01	1.00	LR+	+	-	-	+	+	-	-
015 Chemical B101	0.65	LR+	-	-	-	+	-	-	-
016 Chemical B102	0.65	LR+	+	-	-	-	+	+	+
017 Chemical B103	0.65	LR+	-	-	-	-	-	-	-
018 Chemical B104	0.65	LR+	-	-	-	-	-	-	-
Group C									
019 Chemical C01	-----	LR+	-	-	-	-	-	-	-
020 Chemical C02	-----	LR+	-	+	-	-	-	-	-
021 Chemical C03	-----	LR+	-	-	-	-	-	-	-
022 Chemical C04	-----	LR+	-	-	-	-	-	-	-
023 Chemical C05	-----	LR+	+	-	-	-	-	-	-
024 Chemical C06	-----	LR+	-	-	-	-	-	-	-
025 Chemical C07	-----	LR+	-	+	-	-	-	-	-
026 Chemical C08	-----	LR+	-	-	-	-	-	-	-
027 Chemical C09	-----	LR+	-	-	-	-	-	-	-
028 Chemical C10	-----	LR+	+	-	-	-	-	-	-
029 Chemical C11	-----	LR+	+	-	-	-	-	-	-
030 Chemical C12	1.00	LR+	-	-	-	-	-	-	-
031 Chemical C13	-----	LR+	-	-	-	-	-	-	-
032 Chemical C14	-----	LR+	-	+	-	-	-	-	-
033 Chemical C15	-----	LR+	-	-	-	-	-	-	-
034 Chemical C101	0.90	LR+	-	-	-	-	-	-	-
035 Chemical C102	0.85	LR+	-	+A	-	-I	-I	-I	-I
036 Chemical C103	0.85	LR+	-	-I	-	-I	-I	-I	-I
037 Chemical C104	0.85	LR+	-	+	-	-	-	-	-
038 Chemical C105	0.85	LR+	-	-	-	-	-	-	-
039 Chemical C106	0.45	LR+	-	+	-	-	-	-	-
040 Chemical C107	0.35	LR+	-	+	-	-	-	-	-
Group D									
041 Chemical D01	1.00	LR+	-	-	+	+	+	-	-
042 Chemical D02	-----	LR+	+	-	-	-	-	-	+
043 Chemical D03	-----	LR+	-	-	+	-	-	-	+
044 Chemical D04	-----	LR+	+	-	-	-	-	-	+
045 Chemical D05	-----	LR+	-	-	+	+	+	-	-
046 Chemical D101	0.65	LR+	-	+A	-	-	-	-	-
047 Chemical D102	0.50	LR+	+A	-I	-	-I	-A	-I	+?A

Chemical Name	Toxicological / Adverse Effect Dose					
	8r	8m	9t	9n	10r	10m
	MCASE Rat MTD	MCASE Mouse MTD	MC4PC Human MRTD	MC4PC Human NOEL	MCASE Rat LD50	MCASE Mouse LD50
TEST AND MODEL COMPOUNDS						
Group A						
001 Chemical A01	160	32	4.0	0.40	>5000*	7.4*
002 Chemical A02	150	450	4.0	0.40	5000*	21*
003 Chemical A03	160	470	70	7.0	>5000*	3700*
004 Chemical A04	140	260	6.5	0.65	4800*	5000*
005 Chemical A05	85	32	4.0	0.40	4600*	3500*
006 Chemical A06	520	32	4.0	0.40	3600*	2300*
007 Chemical A07	520	120	4.0	0.40	3500*	2300*
008 Chemical A08	340	80	4.0	0.40	4600*	1200*
009 Chemical A09	250	140	4.0	0.40	3500*	2300*
010 Chemical A101	150	32	4.0	0.40	3300*	720*
011 Chemical A102	150	450	4.0	0.40	5000*	21*
012 Chemical A103	94	0.0020 [†]	4.9	0.49	>5000*	2100*
013 Chemical A104	8.0	500	38	3.8	3600*	>5000*
Group B						
014 Chemical B01	160	>5000	6.7	0.67	1100	>5000
015 Chemical B101	96	200	0.50	0.050	1100	1500
016 Chemical B102	130	1600	4.0	0.40	3800	>5000
017 Chemical B103	70	140	1.7	0.17	3600	>5000
018 Chemical B104	1500	3500	1.1	0.11	3200	>5000
Group C						
019 Chemical C01	750	50	0.80	0.080	4700	>5000
020 Chemical C02	39	16	0.050	0.0050	4700	3900
021 Chemical C03	150	16	10	1.0	3400	3700
022 Chemical C04	19	6900	5.0	0.50	>5000	>5000
023 Chemical C05	340	16	17	1.7	4700	1300
024 Chemical C06	70	16	1.7	0.17	3300	>5000
025 Chemical C07	0.67	140	4.0	0.40	3700	1500*
026 Chemical C08	70	16	1.5	0.15	3300*	>5000*
027 Chemical C09	70	16	0.090	0.0090	>5000	>5000
028 Chemical C10	70	210	0.40	0.040	3700	>5000
029 Chemical C11	17	940	0.40	0.040	1100	160
030 Chemical C12	14	1300	4.0	0.40	2400	>5000
031 Chemical C13	14	1300	4.0	0.40	4600	3500
032 Chemical C14	15*	1300*	4.0	0.40	2400	>5000*
033 Chemical C15	70	16	4.0	0.40	4000	>5000
034 Chemical C101	70	16	0.050	0.0050	4600	>5000
035 Chemical C102	70 (50 Expt.)	450 (500 Expt.)	0.63 (Expt. 0.33)	0.063	3000	>5000
036 Chemical C103	70	16	0.050 (Expt. 0.10)	0.0050	>5000	>5000
037 Chemical C104	70	450	0.63	0.063	4600	>5000
038 Chemical C105	70	16	0.050	0.0050	4700	3200
039 Chemical C106	70	16	4.0	0.40	4700	>5000
040 Chemical C107	70	1600	4.0	0.40	3700	>5000
Group D						
041 Chemical D01	130	48	5.2	0.52	3500*	3200*
042 Chemical D02	70	45	6.7	0.67	>5000*	3500*
043 Chemical D03	70	45	0.40	0.040	3500*	1400*
044 Chemical D04	70	45	7.5	0.75	4200*	3500*
045 Chemical D05	130	40	4.0	0.40	920*	3200*
046 Chemical D101	70	320	4.0	0.40	>5000	1500*
047 Chemical D102	26 (25 Expt.)	45 (50 Expt.)	0.0030 ^{†a}	0.00030 [†]	560*	3400*

^aExpt. 0.010

ABBREVIATIONS and DEFINITIONS: (A more complete list of abbreviations and definitions is provided in a glossary as the last item of this report.) In **Table 0** the *MC4PC* predicted toxicological activities are coded: "+" (positive containing ≥ 2 structurally similar alerts), "+?" (possibly active containing ≥ 2 structurally similar (or dissimilar) alerts that were rejected based upon human expert system assay evaluation rules), or "-" (negative). "*" is shown for chemicals for which poor coverage was observed. "†" is shown for predictions which exhibit high statistical variance. Positive calls on molecules with poor coverage are still counted as positive since the presence of a known structural alert is not negated by the additional presence of unknown fragments in other parts of the molecule. However, negative predictions with unknown fragments (*i.e.*, "-*") are counted as a "no call" since the unknown fragment might actually be positive.

Actual experimental toxicological activities (or clinical effects) are coded: "A" (active), "I" (inactive), and "M" (marginal). An active response ("A") is reserved for experimental activities that are

biologically/statistically significant at two or more related endpoints (*i.e.*, *trans*-gender/species carcinogenicity, *trans*-species teratogenicity, adverse immunological effects at ≥ 2 endpoints, *etc.*); A marginal response (“**M**”) is assigned to an equivocal/weak activity that is of questionable biological/statistical significance. Note that no distinction is made among stereo or geometrical isomeric variations of the test, model or training compounds when activity (or lack of activity) is attributed to chemical substances.

Abbreviations for the different toxicological endpoints include: (1) “**Carc.**” (carcinogenicity in rodents: rats and mice); (2) “**Terat.**” (teratogenicity in mammals: rabbits, rats and mice); (3) “**Salm.**” (mutagenicity in *Salmonella typhimurium*); (4) “**Liver**” (adverse liver side effects in adult humans); (5) “**Imm.**” (adverse immunological side effects in adult humans); (6) “**Kid.**” (adverse kidney side effects in adult humans); and (7) “**Card.**” (adverse cardiological side effects in adult humans).

Additional abbreviations include: “**\$\$\$**” (proprietary compound and data); “**S.I.**” (similarity index measure of structural similarity determined by *ISIS™/HOST* software); and “**Bio.**” (bioavailability determined by the *MC4PC* software).

II. RESULTS

A. NON-CLINICAL TOXICOLOGICAL ACTIVITIES

1. Carcinogenicity Findings: Table 1 contains a summary of the *MC4PC* predicted activities and actual experimentally determined carcinogenic activities of the forty-seven (47) compounds. The prediction of carcinogenicity in rodents is based upon results of toxicology studies in the FDA/CDER, NIEHS, NCI, and L. Gold CPD databases, as well as the published literature. Seven *MC4PC* modules have been constructed to evaluate carcinogenicity in rodents: **AD1** (rodents, Ro), **AD2** (rats, Ra), **AD3** (male rat, MR), **AD4** (female rat, FR), **AD5** (mice, Mi), **AD6** (male mouse, MM), and **AD7** (female mouse, FM). Modules **AD2-AD7** are used in the *MC4PC* rodent carcinogenicity tests, and predictions using the standalone modules **AD1** are available upon request. The materials and methods and the results of a validation test have been described for *MCASE* (Matthews, E.J. and Contrera, J.F. A new highly specific method for predicting the carcinogenic potential of pharmaceuticals in rodents using enhanced *MCASE-ES* software. *Regulatory Toxicology and Pharmacology* **28**:242-264, 1998).

Based upon our assay evaluation criteria for interpreting the results of the six *MC4PC* rodent carcinogenicity database modules, twenty-nine (29/47) compounds are not evaluated as active in the *MC4PC* rodent carcinogenicity test (Table 1). In contrast, ten (10/47) compounds are predicted to be *trans*-gender and/or *trans*-species rodent carcinogens based upon the presence of two or more biologically significant, structurally similar alerts (**SSA**). The alerts correspond to the following fragments: {fragment #01}; {fragment #02}; {fragment #03}; and {fragment #22}. Addendum Table 1 shows detailed information about these fragments. In addition, eight (8/47) compounds containing ≥ 2 structurally similar or dissimilar alerts are evaluated as possibly active based upon human expert system assay evaluation rules. One (1/47) compound has been experimentally tested for carcinogenicity in rodents and was shown to be positive. All forty-seven (47/47) compounds had adequate coverage in this *MC4PC* test.

2. Teratogenicity Findings: Table 2 contains a summary of the *MC4PC* predicted activities and actual experimentally determined teratogenic activities of forty-seven (47) compounds. The prediction of teratogenicity in mammals is based upon results of toxicology studies in the FDA/CDER, NIEHS, NCI, TERIS, SHEPARDS, REPROTOX, and RTECS databases, as well as studies in the published literature and the *Physicians' Desk Reference* (PDR). The *MC4PC* Mammalian Teratogenicity Test includes five different database modules: **A50** (rabbits, Rab.), **A51** (rats), **A52** (mice), **A53** (mammals, Mam.), and **A54** (rodents, Rod.). The **A53** mammalian database module contains studies from all mammalian species, including the rabbit, rat and mouse studies used in the **A50-A52** modules, and the **A54** rodent database module contains studies from only the rabbit, rat and mouse. Each was treated as an independent experiment for assessing the teratogenic potential of organic chemicals in mammals and rodents, respectively.

The results obtained from the five teratogenicity database modules showed that thirty-nine (39/47) compounds are not predicted to be *trans*-species mammalian teratogen in the *MC4PC* Mammalian Teratogenicity Test. In contrast, eight (8/47) compounds contained two or more biologically significant, structurally similar alerts (**SSA**) and are predicted to be mammalian teratogens. The alerts correspond to the following fragments: {fragment #04}; {fragment #05}; {fragment #23}; {fragment #07}; and {fragment

#08}. **Addendum Table 2** shows detailed information about these fragments. Two (2/47) compounds have been experimentally tested for teratogenicity in mammals and were found to be positive, and a further two (2/47) compounds have been experimentally tested and were found to be negative. The forty-seven (47/47) compounds had adequate coverage in this *MC4PC* test.

3. Mutagenicity in Bacteria Findings: **Table 3** contains a summary of the *MC4PC* predicted activities and actual experimentally determined mutagenic activities of forty-seven (47) compounds in the *Salmonella typhimurium* mutagenicity assay. This table presents the activities of four procaryote tester strains: TA100 (mutations at *hisG46*, *rfa*, and *uvrB*: R-factor plasmid *pkM-101*); TA1535 (mutations at *hisG46*, *rfa*, *uvrB*); TA1537 (mutations at *hisC3076*, *rfa*, and *uvrB*); and TA98 (mutations at *hisC3052*, *rfa*, and *uvrB*: R-factor plasmid *pkM-101*). TA100 and TA1535 detect base pair substitution mutations; TA1537 and TA98 detect frameshift mutations. The activities of the test and model compounds are presented for each tester strain under four different experimental conditions: (1) mutagenic activity with no S9 microsomal activation system using modules **A6K** (TA100), **A6L** (TA1535), **A6M** (TA1537), and **A6O** (TA98); (2) mutagenic activity with rat liver S9 present using modules **A6P** (TA100), **A6R** (TA1535), **A6S** (TA1537), and **A6U** (TA98); (3) mutagenic activity with hamster liver S9 present using modules **A6V** (TA100), **A6W** (TA1535), **A6X** (TA1537), and **A6Z** (TA98); and (4) overall mutagenic activity in the presence and absence of S9 using module **A2J** (TA 100 + TA1535 + TA1537 + TA97 + TA98).

The results of these four different groups of database modules in the *MC4PC Salmonella typhimurium* Mutagenicity Test were treated as independent experiments for assessing the mutagenic potential of organic chemicals in *Salmonella typhimurium*.

The modules used for the prediction of mutagenicity in procaryotes are based upon results of toxicology studies conducted by the NIEHS/NTP, studies performed by industry and submitted to FDA/CDER, data acquired from PhRMA and the scientific literature by MultiCASE, Inc. under a NIH research grant, and additional studies from the Zeiger database. The results of the studies were entered based upon the original revertant frequency data, and positive responses were weighted and are proportional to the log-normalized, fold-increase of revertants over the background response of each strain. This experimental approach permits analysis of the mechanism of mutagenesis (base-pair shift vs. substitution) and mutagenic potency. Predictions using these modules are not based upon activities of several other tester strains, such as TA97, TA102, TA104, and *E. coli* WP2, because the data sets for these strains are currently too small to model.

The results obtained from the thirteen mutagenicity database modules showed that in the absence and in the presence of rat liver or hamster liver S9 activation system, forty-two (42/47) compounds are not predicted to be active in the *MC4PC Salmonella typhimurium* Mutagenicity Test (\pm S9) and are not predicted to be either base-pair or frameshift mutagens. In contrast, three (3/47) compounds contained two or more biologically significant, structurally similar alerts (**SSA**) and are predicted to be *Salmonella* mutagens. The alerts correspond to the following fragments: {*fragment #09*}; {*fragment #10*}; and {*fragment #11*}. **Addendum Table 3** shows detailed information about these fragments. Forty-five (45/47) compounds had adequate coverage in this *MC4PC* test but two (2/47) had inadequate coverage and no structural alerts and were considered “no calls.”

B. CLINICAL ADVERSE EFFECTS

We are currently developing *MC4PC* modules that are designed to predict the potential organ and organ system adverse effects of organic chemicals in adult humans. These modules are exclusively based upon post-marketing adverse effects report data obtained from the FDA/CDER Spontaneous Reporting System that were recorded between 1969 and October, 1997. This is a large, non-proprietary database containing over 1,500,000 adverse drug reaction reports. The adverse effects are described using a standardized vocabulary employing 1168 different COSTAR (COding Symbols for the Thesaurus of Adverse Reaction) clinical terms. For the purposes of modeling, COSTAR terms are grouped by organ system and then divided into sub-groups of highly concordant endpoints. This allows identification of structural alerts with greater statistical significance and enhances the predictive performance of *MC4PC*. [These modules do not contain pre-market clinical trial data reported in labeling, or data derived from the FDA/CDER Adverse Event Reporting Systems (AERS) database (November, 1997 forward). The latter uses different terminology to describe adverse effects and will be the subject of other investigations.] The modules do not contain proprietary clinical data from either Agency or pharmaceutical industry archives. The materials, methods, and results of validation tests will be reported in detail upon their completion.

1. Adverse Liver Effect Findings: The adverse liver effect findings of pharmaceuticals in the

FDA/CDER Spontaneous Reporting System (SRS) database are summarized using forty-seven (47) different COSTAR terms. The adverse liver side effects include anatomical, histological and/or pathological terms and, with the exception of two terms, are divided into five categories. The adverse liver side effect data were used to construct a total of fourteen (14) *MC4PC* modules. Five of the modules were constructed to estimate liver enzyme effects: **A11** (alkaline phosphatase increase); **A12** (SGOT increase); **A13** (SGPT increase); **A15** (gamma glutamyl transpeptidase increase); and **A10** (combined liver enzyme effects). Four *MC4PC* modules were constructed to estimate liver obstruction: **A17** (bilirubinemia); **A18** (jaundice); **A19** (jaundice cholestatic); and **A16** (combined liver obstruction effects). Three *MC4PC* modules were constructed to estimate liver pathology: **A22** (liver failure); **A23** (liver damage); **A21** (combined liver pathology effects). One *MC4PC* module was constructed to estimate abnormal liver function (**A24**) and one module was constructed to estimate hepatitis (**A25**). We are including in this report predictions made using modules **A10-A13**, **A15-A19**, and **A21-A23**; predictions using modules **A24** and **A25**, which are standalone adverse effect endpoints, are available upon request.

Table 4 contains a summary of the *MC4PC* predicted activities and actual reported adverse liver side effects of forty-seven (47) compounds in adult humans. Based upon our assay evaluation criteria, forty-one (41/47) compounds are not evaluated as active in the *MC4PC* Adverse Liver Effects Test and are not predicted to exhibit adverse liver effects in adult humans. Three (3) of these compounds were present in the training data set and scored as inactive. In contrast, four (4/47) compounds contained two or more biologically significant, structurally similar alerts (**SSA**) and are predicted to cause adverse liver side effects in adult humans. The alerts correspond to the following fragments: {*fragment #12*}; {*fragment #13*}; {*fragment #14*}; and {*fragment #15*}. Forty-five (45/47) compounds had adequate coverage in this *MC4PC* test but two (2/47) had inadequate coverage and no structural alerts and were considered “no calls.”

2. Adverse Immunological Effect Findings: The adverse immunological effect findings of pharmaceuticals in the FDA/CDER Spontaneous Reporting System (SRS) database are summarized using eighty-one (81) different COSTAR terms. The adverse immunological side effects include adverse anatomical, histological and/or pathological terms, and are divided into four separate categories. The adverse immunological effect data were used to construct a total of sixteen (16) *MC4PC* modules. Eight modules were used to estimate bone marrow effects: **A31** (leukopenia); **A32** (pancytopenia); **A39** (leukocytosis); **A40** (agranulocytosis); **A41** (marrow depression); **A42** (eosinophilia); **A43** (lymphadenopathy); and **A30** (combined bone marrow effects). Six modules were used to estimate adverse effects of the skin: **A34** (rash); **A35** (pruritus); **A36** (urticaria); **A37** (allergic reaction); **A38** (facial edema); and **A33** (combined adverse skin effects). One module was constructed to estimate anaphylaxis (**A28**) and one module was constructed to estimate asthma (**A29**). We are including in this report predictions made using modules **A30-A38** and **A40-A42**; predictions using modules **A28**, **A29**, **A39** and **A43**, which are standalone adverse effect endpoints, are available upon request.

Table 5 contains a summary of the *MC4PC* predicted activities and actual reported adverse immunological effects of forty-seven (47) compounds in adult humans. Based upon our assay evaluation criteria, forty (40/47) compounds are evaluated as inactive in the *MC4PC* Adverse Immunological Effects Test and are not predicted to exhibit adverse immunological effects in adult humans. Three (3) of these compounds were present in the training data set, two (2) of which were scored as inactive and one (1) of which was scored active at a single endpoint. In contrast, five (5/47) compounds contained two or more biologically significant, structurally similar alerts (**SSA**) and are predicted to cause adverse immunological side effects in adult humans. The alerts correspond to the following fragments: {*fragment #16*}; {*fragment #17*}; and {*fragment #18*}. Forty-five (45/47) compounds had adequate coverage in this *MC4PC* test but two (2/47) had inadequate coverage and no structural alerts and were considered “no calls.”

3. Adverse Kidney Effect Findings: The adverse kidney and urinary tract effect findings of pharmaceuticals in the FDA/CDER Spontaneous Reporting System (SRS) database are summarized using seventy-four (74) different COSTAR terms. The adverse kidney and urinary tract side effects include adverse anatomical, histological and/or pathological terms and, with the exception of fourteen (14) terms, are divided into two separate categories. The adverse kidney and urinary tract effect data were used to construct a total of thirteen (13) *MC4PC* modules. Five of the modules are constructed to estimate adverse urinary tract effects: **A1I** (urinary retention); **A1J** (urinary incontinence); **A1K** (urinary frequency); **A1L** (dysuria); and **A1H** (combined adverse urinary tract and bladder effects). Eight of the modules were constructed to estimate adverse kidney function effects: **A1B** (acute kidney failure); **A1C** (kidney failure); **A1D** (hematuria); **A1E** (BUN increase); **A1F** (creatinine increase); **A1G** (abnormal kidney function); **A1M** (edema), and **A1A** (combined kidney function endpoints). We are including in this report predictions made using the modules **A1A-A1L**; predictions using the standalone module **A1M**, are available upon request.

Table 6 contains a summary of the *MC4PC* predicted activities and actual reported adverse kidney side effects of forty-seven (47) compounds in adult humans. Based upon our assay evaluation criteria, thirty-four (34/47) compounds are not evaluated active in the current *MC4PC* Adverse Kidney Effects Test and are not predicted to cause adverse kidney effects in adult humans. Three (3) of these compounds were present in the training data set and scored as inactive. In contrast, four (4/47) compounds contained two or more biologically significant, structurally similar alerts (**SSA**) and are predicted to cause adverse kidney side effects in adult humans. The alerts correspond to the following fragment: {*fragment #19*}. A further two (2/47) compounds were evaluated as possibly active for adverse kidney side effects based on our assay evaluation criteria. Thirty-seven (37/47) compounds had adequate coverage in this *MC4PC* test but ten (10/47) compounds had inadequate coverage. Of these latter ten (10) compounds, seven (7) had no structural alerts and were considered “no calls.”

4. Adverse Cardiological Effect Findings: The adverse heart and cardiovascular system effect findings of pharmaceuticals in the FDA/CDER Spontaneous Reporting System (SRS) database are summarized using one hundred and thirty-two (132) different COSTAR terms. The adverse cardiological side effects include anatomical, histological and functional terms and, with the exception of sixteen (16) terms, are subdivided into five separate categories. The cardiological adverse effect data records were used to construct a total of twenty-one (21) *MC4PC* database modules. Four *MC4PC* modules were constructed to estimate adverse heart pathology effects: **AI2** (heart arrest); **AI3** (heart failure); **AI4** (right heart failure); and **AI1** (combined adverse heart pathology effects). Six of the modules estimate adverse conduction effects on the heart: **AI7** (bradycardia); **AI8** (tachycardia); **AJ1** (palpitation); **AJ2** (arrhythmia); **AJ3** (atrial fibrillation); and **AI9** (combined arrhythmia endpoints). Five of the modules estimate hypotension and related effects: **AJ6** (hypotension); **AJ7** (vasodilation); **AJ8** (shock); **AJ9** (syncope); and **AJ5** (combined hypotension and related effects). Five of the modules are constructed to estimate circulation abnormality: **AI6** (myocardial infarct); **AK1** (cerebrovascular accident); **AK2** (pulmonary embolus); **AK3** (cardiovascular disorder); and **AI5** (combined abnormal circulation endpoints). Finally, one module was constructed to estimate hypertension (**AJ4**). We are including in this report predictions made using modules **AI1-AI3**, **AI5**, **AI6**, **AI8**, **AJ1**, **AJ2**, **AJ5-AJ9**, and **AK1**; predictions using modules **AI4**, **AI7**, **AI9**, **AJ3**, **AJ4**, **AK2**, and **AK3**, which have a low percentage of positives or are standalone adverse effect endpoints, are available upon request.

Table 7 contains a summary of the *MC4PC* predicted activities and actual reported adverse cardiological side effects of forty-seven (47) compounds in adult humans. Based upon our assay evaluation criteria, twenty-nine (29/47) compounds are evaluated as inactive in the current *MC4PC* Adverse Cardiological Effects Test and are not predicted to exhibit adverse cardiological side effects in adult humans. Two (2) of these compounds were present in the training data set and scored as inactive. In contrast, eleven (11/47) compounds contained two or more biologically significant, structurally similar alerts (**SSA**) and are predicted to cause adverse cardiological side effects in adult humans. The alerts correspond to the following fragments: {*fragment #20*}; and {*fragment #21*}. A further seven (7/47) compounds were evaluated as possibly active for adverse cardiological side effects based on our assay evaluation criteria, one of which was present in the training data set and scored as active. Thirty-seven (37/47) compounds had adequate coverage in this *MC4PC* test but ten (10/47) compounds had inadequate coverage.

C. TOXICOLOGICAL DOSE

1. Maximum Tolerated Dose (MTD) Findings: **Table 8** contains a summary of the *MCASE* predicted activities and actual experimentally determined maximum tolerated dose (MTD) values of forty-seven (47) compounds. The prediction of the MTD of organic chemicals in rodents is based upon data obtained from lifetime (two year) carcinogenicity studies in the NIEHS, NCI, and L. Gold CPD databases, as well as in the published literature. The *MCASE* Maximum Tolerated Dose (MTD) Test includes a total of eight different database modules in order to detect potential gender-specific and species-specific toxicities of compounds which had either high or low toxicity in rodents. The eight individual modules are: **A81** (high toxicity in male rats, MR); **A82** (high toxicity in female rats, FR); **A83** (high toxicity in male mice, MM); **A84** (high toxicity in female mice, FM); **A77** (low toxicity in male rats, MR); **A78** (low toxicity in female rats, FR); **A79** (low toxicity in male mice, MM); and **A80** (low toxicity in female mice, FM).

Based upon our assay evaluation criteria for interpreting the combined results of eight MTD database modules, the forty-seven (47) compounds are estimated to have a range of MTD values of 0.67 to 1500 mg/kg-bw/day in rats, and 0.0020 to >5000 mg/kg-bw/day in mice. Two (2/47) of these compounds have been experimentally evaluated for the MTD in both rats and mice. One (1/47) compound was inadequately covered in both rats and mice and one compound (1/47) exhibited high statistical variance in mice.

2. Maximum Recommended Therapeutic Dose (MRTD) and No Effect Level (NOEL) Findings:

Table 9 contains a summary of the *MC4PC* predicted maximum recommended therapeutic dose (MRTD) and no effect level (NOEL) values of two compounds. The prediction of the MRTD values for pharmaceuticals and NOEL dose values of organic chemicals in adult humans is based upon MRTD data from human clinical trials for pharmaceuticals. The NOEL is considered the MTD for organic chemicals that are not intended to alter the structure or function of the human body (*i.e.*, non-pharmaceuticals), and it is estimated using the equation: $NOEL = MRTD/10$. The *MC4PC* Maximum Recommended Therapeutic Dose (MRTD) and No Effect Level (NOEL) Tests each include two different database modules in order to detect potential toxicities of compounds which had either high or low toxicity in adult humans. The two individual modules are: **A95** (high toxicity in adult humans), and **A97** (low toxicity in adult humans). The materials and methods and the results of the *MC4PC* validation test have been described (see Matthews, E.J., Kruhlak, N.L., Benz, R.D., and Contrera, J.F. Assessment of the health effects of chemicals in humans: I. QSAR estimation of the maximum recommended therapeutic dose (MRTD) and no effect level (NOEL) of organic chemicals based on clinical trial data, *Current Drug Discovery Technologies*, 1:61-76, 2004.).

Based upon our assay evaluation criteria for combining the results of two MRTD database modules, the forty-seven (47) compounds are estimated by *MC4PC* to have a range of MRTD values from 0.0030 to 70 mg/kg-bw/day, and a range of NOEL dose values from 0.00030 to 7.0 mg/kg-bw/day. Furthermore, the actual experimental dose value for three compounds has already been determined. One compound (1/47) exhibited high statistical variance between predicted values. All forty-seven (47) compounds had adequate coverage in this *MC4PC* test.

3. Acute Toxicity Findings: **Table 10** contains a summary of the *MC4PC* predicted activities and actual experimentally determined acute toxicity (LD_{50}) values of forty-seven (47) compounds. The prediction of the acute toxicity of organic chemicals in rats and mice is based upon data obtained from acute toxicity studies in the FDA/CFSAN PAFA database and a WHO database of acute toxicity studies for pesticides, as well as in the published literature. The *MC4PC* Test includes a total of four different database modules in order to detect potential species-specific toxicities of compounds which had either high or low toxicity in rodents. The four individual modules are: **AL1** (high toxicity in rats); **AL2** (low toxicity in rats); **AL3** (high toxicity in mice); and **AL4** (low toxicity in mice).

Note that the current database modules are deficient in acute toxicity studies for pharmaceuticals. The next versions of the **AL1-AL4** modules will contain acute toxicity data from FDA/CDER archives to overcome this deficiency. In addition, the current mouse **AL3-AL4** database modules have a relatively small training data set of compounds (n=410) compared to the rat **AL1-AL2** database modules (n=1304). Because of this, predictions for acute toxicity in mice should be considered less reliable.

Based upon our assay evaluation criteria for combining the results of four acute toxicity database modules, the forty-seven (47) compounds are estimated to have acute toxicity values from 560 to >5000 mg/kg-bw in rats, and from 7.4 to >5000 mg/kg-bw in mice. Twenty-six (26/47) compounds had adequate coverage in rats and twenty-three (23/47) compounds had adequate coverage in mice.

COMMENTS: This report includes summary information and does not include all of the *in silico* experimental data generated; complete *in silico* data sets are maintained by FDA/CDER. All test compound structures and associated *in silico* experimental data upon which this report is based are being treated as proprietary.

Table 1: Summary of the MC4PC Estimated and Actual Carcinogenic Activities of Forty-seven (47) Compounds in Rats and Mice

MC No. ^a Compound Name ^b	Structural Alerts / Carcinogenicity Modules ^c						Expert Opinions		
	AD2	AD3	AD4	AD5	AD6	AD7	No	Overall	
	Ra	MR	FR	Mi	MM	FM	SSA ^d	Call ^e	
TEST AND MODEL COMPOUNDS									
Group A									
001 Chemical A01	-Bb	-Bbd	+Bd	-	-	-	3	+?	qsar
002 Chemical A02	+Bb	+BB?bd	+2Bd	-	-	-	3	+	
003 Chemical A03	-Bb	-Bbd	-Bd	-	-	-	3	-	de qsar
004 Chemical A04	-w	-dw	-dw	-w	-w	-w	0	-	
005 Chemical A05	-Bb	-Bbd	-Bd	-B	+B	-	5	+?	de qsar
006 Chemical A06	-Bbw	-Bbdw	-Bdw	-w	-w	-w	3	-	de
007 Chemical A07	+BB?b	-Bbd	-2Bd	-	-	-	5	+?	de qsar
008 Chemical A08	-BbDw	-Bbdw	-BDdw	+Bw	-w	-w	3	+?	de
009 Chemical A09	-2BbD	-Bbd	-2BDd	+B	-	-	5	+?	de qsar
010 Chemical A101	+Bb	-Bbd	+Bd	-	-	-	3	+	
011 Chemical A102	+Bb	+BB?bd	+2Bd	-	-	-	3	+	
012 Chemical A103	+Bbw	-Bbdw	+Bbdw	-w	-w	-w	3	+	
013 Chemical A104	-B	-B	-B	+B	-B	-B	6	+?	de qsar
Group B									
014 Chemical B01	+B	+B	+B	+B	-	+B	4	+	
015 Chemical B101	-D	-D	-D	-	-	-	0	-	
016 Chemical B102	+B	+B	+B	+B	-	+B	4	+	
017 Chemical B103	-D	-D	-D	-	-	-	0	-	
018 Chemical B104	-D	-D	-D	-	-	-	0	-	
Group C									
019 Chemical C01	-	-	-	+B?	-Dd	-D	1	-	
020 Chemical C02	-	-	-	-B?	-2d	-	0	-	
021 Chemical C03	-D	-D	-D	-	-d	-	0	-	
022 Chemical C04	-	-	-	-	-d	-	0	-	
023 Chemical C05	-	+B?	-	-	+Bd	+BB?	2	+	
024 Chemical C06	-D	-D	-Dd	-d	-	-	0	-	
025 Chemical C07	-	-	-d	-b	-	-	0	-	
026 Chemical C08	-w	-w	-dw	-w	-dw	-w	0	-	
027 Chemical C09	-D	-D	-D	-	-	-	0	-	
028 Chemical C10	-	+B?	-	-	+B	+BB?	3	+	
029 Chemical C11	-B	+BB?	-	-d	+B	+BB?	3	+	
030 Chemical C12	-B	-B	-	-2d	-2d	-	2	-	deg qsar
031 Chemical C13	-B	-B	-	-2d	-2d	-	2	-	deg qsar
032 Chemical C14	-Bw	-Bw	-w	-2dw	-2dw	-w	2	-	deg qsar
033 Chemical C15	-Bw	-Bw	-w	-2dw	-2dw	-w	2	-	deg qsar
034 Chemical C101	-	-	-	-d	-2d	-	0	-	
035 Chemical C102	-	-	-	-B	-	-b	0	-	
036 Chemical C103	-	-	-	-	-d	-	0	-	
037 Chemical C104	-	-	-	-Bd	-d	-b	0	-	
038 Chemical C105	-	-	-	-	-d	-	0	-	
039 Chemical C106	-	-	-d	-	-d	-	0	-	
040 Chemical C107	-	-	-d	-	-	-	0	-	
Group D									
041 Chemical D01	-	-	-	-B?D	-D	-	0	-	
042 Chemical D02	+B2B?	-2B	-B	-d	-2d	-d	5	+?	de deg qsar
043 Chemical D03	-2B	-B	-B	-d	-d	-d	3	-	de qsar
044 Chemical D04	+BB?	+BB?	-B	-d	-d	-d	3	+?	de qsar
045 Chemical D05	-	-	-	-B?Dd	-D	-	0	-	
046 Chemical D101	+Bb	+Bb	+B	-	-	-2d	1	-	
047 Chemical D102	+BA	+BA	+BA	-BA	-BA	-BA	6	+A	

LEGEND TO TABLE 1

^a**MC No.:** The *MC4PC* program automatically counts and enumerates each of the test compounds being analyzed.

^b**Compound Name:** The name of the test compound being analyzed in the *MC4PC* QSAR tests.

^c**Structural Alerts / Carcinogenicity Modules:** An explanation for the different codes for molecular structural alerts identified by the *MC4PC* system is provided in a glossary at the end of this report. Additional information on the rodent carcinogenicity database modules **AD2-AD7** is provided in **Section II.A.1**.

^d**No. SSA:** The total number of structurally similar alerts (**SSA**) identified by *MC4PC* in the test compound is used to predict the carcinogenic potential of the test compound. The SSA value refers to the SSA identified using the modules **AD2-AD7**.

^e**Overall Call:** The expert opinion call refers to the evaluation of the activity of the test compound, including: "+", active compounds have ≥ 2 SSA; "-", inactive compounds have < 2 SSA; and "+?" for compounds that are possibly active. See the glossary at the end of this report for other codes.

Table 2: Summary of the MC4PC Estimated and Actual Teratogenic Activities of Forty-seven (47) Compounds in Mammals

MC No. ^a Compound Name ^b	Structural Alerts / Teratogenicity Modules ^c					Expert Opinions	
	A50 Rab.	A51 Rats	A52 Mice	A53 Mam.	A54 Rod.	No. SSA ^d	Overall Call ^e
TEST AND MODEL COMPOUNDS							
Group A							
001 Chemical A01	-2d	-Bb	-	-d	-	0	-
002 Chemical A02	-2d	-Bb	-	-d	-	0	-
003 Chemical A03	-D2d	-bd	-	-d	-d	0	-
004 Chemical A04	-Ddw	+Bb	-d	-	-	1	-
005 Chemical A05	-2d	-bD	-	-Dd	-D	0	-
006 Chemical A06	-3dw	-bw	-w	-Ddw	-Dw	0	-
007 Chemical A07	-3d	-b	-d	-Dd	-D	0	-
008 Chemical A08	-dw	-w	-w	-BDdw	-Dw	0	-
009 Chemical A09	-d	-	-bdw	-BDd	-D	0	-
010 Chemical A101	-d	-Bb	-	-d	-	0	-
011 Chemical A102	-2d	-Bb	-	-d	-	0	-
012 Chemical A103	-dw	-bw	-w	-w	-bw	0	-
013 Chemical A104	-D	-	-d	-2Bbd	-	1	-
Group B							
014 Chemical B01	-	-B	-B	-B	-B	4	- deg
015 Chemical B101	-d	-	-	-	-	0	-
016 Chemical B102	-	-B	-B	-B	-Bb	4	- deg
017 Chemical B103	-	-	-	-	-	0	-
018 Chemical B104	-Dd	-	-d	-	-	0	-
Group C							
019 Chemical C01	-d	-d	-bd	+2BB?	-d	1	-
020 Chemical C02	+B?	+BB?	-bd	+2B2B?	+B	3	+
021 Chemical C03	+B?d	-d	-bd	+2B2B?	-bd	1	-
022 Chemical C04	-d	-d	-b2d	+2BB?	-d	1	-
023 Chemical C05	+B?2d	-	-d	-d	-d	1	-
024 Chemical C06	-	-d	+B	-	-	1	-
025 Chemical C07	-	-d	+2B	+2B	-	4	+
026 Chemical C08	-Dw	-dw	+Bw	-w	-dw	1	-
027 Chemical C09	-B	-	-	-	-	0	-
028 Chemical C10	-3d	-	-d	-d	-d	0	-
029 Chemical C11	-3d	-	-	-d	-	0	-
030 Chemical C12	-d	-d	-	-	-	0	-
031 Chemical C13	-	-d	-	-	-	0	-
032 Chemical C14	-xw	+B	-	+B	-B	3	+
033 Chemical C15	-w	-dw	-w	-w	-w	0	-
034 Chemical C101	-d	-d	-d	-	-d	0	-
035 Chemical C102	+BA	-dM	+BA	+BA	+BA	4	+A
036 Chemical C103	-Bdl	-l	-d	-l	-dl	0	-l
037 Chemical C104	+B	-d	-	-	+B	2	+
038 Chemical C105	-dw	-w	-B?d	-B?	-B?d	3	- deg
039 Chemical C106	-d	-2d	+2B	+2B	-d	4	+
040 Chemical C107	-	-2d	+2B	+2B	-	4	+
Group D							
041 Chemical D01	-	-D	-b2d	-D	-b	0	-
042 Chemical D02	-	-	-w	+Bd	-	1	-
043 Chemical D03	-	-	-w	+Bd	-	1	-
044 Chemical D04	-	-	-w	+Bd	-	1	-
045 Chemical D05	-	-D	-b2d	-D	-	0	-
046 Chemical D101	-	-bA	-	+BA	+BA	2	+A
047 Chemical D102	-l	-dl	+Bw	-dl	-dl	1	-l

LEGEND TO TABLE 2

^a**MC No.:** The *MC4PC* program automatically counts and enumerates each of the test compounds being analyzed.

^b**Compound Name:** The name of the test compound being analyzed in the *MC4PC* QSAR tests.

^c**Structural Alerts / Teratogenicity Modules:** An explanation for the different codes for molecular structural alerts identified by the *MC4PC* program is provided in a glossary at the end of this report. Additional information on the individual mammalian teratogenicity database modules **A50-A54** is provided in **Section II.A.2**.

^d**No. SSA:** The total number of structurally similar alerts (**SSA**) identified by *MC4PC* in the test compound is used to predict the teratogenic potential of the test compound. The SSA value refers to the SSA identified using the **A50-A54** modules.

^e**Overall Call:** The expert opinion call refers to the evaluation of the activity of the test compound, including: '+', active compounds have ≥ 2 SSA; '-', inactive compounds have < 2 SSA; and '+?' for compounds that are possibly active. See the glossary at the end of this report for other codes.

Table 3: Summary of the MC4PC Estimated and Actual Mutagenic Activities of Forty-seven (47) Compounds in *Salmonella typhimurium*

MC No. ^a Compound Name ^b	Structural Alerts / <i>Salmonella t.</i> Mutagenicity Modules ^c												Expert Opinions		
	A2J Comb.	A6K 100	A6L 1535	A6M 1537	A6O 98	A6P 100	A6R 1535	A6S 1537	A6U 98	A6V 100	A6W 1535	A6X 1537	A6Z 98	No. SSA ^d	Overall Call ^e
TEST AND MODEL COMPOUNDS															
Group A															
001 Chemical A01	-w	-3D	-	-w	-D	-w	-Bw	-5w	-Dw	-Dd	-	-w	-D	0	-
002 Chemical A02	-w	-2D	-	-w	-D	-w	-Bw	-5w	-Dw	-d	-	-w	-2D	0	-
003 Chemical A03	-D	-3D	-	-	-	-dw	-w	-3w	-Dw	-2D2d	-	-	-2D	0	-
004 Chemical A04	-	-2Dw	-w	-w	-	-Dd2w	-2w	-3w	-D2w	-2D2dw	-w	-w	-D	0	-
005 Chemical A05	-w	-4D	-	-w	-D	-w	-Bw	-4w	-Dw	-Dd	-	-w	-D	0	-
006 Chemical A06	-2w	-3Dw	-w	-2w	-Dw	-4w	-B4w	-7w	-D4w	-Ddw	-w	-2w	-Dw	0	-*
007 Chemical A07	-w	-3D	-	-w	-D	-4w	-B4w	-7w	-D4w	-Dd	-	-w	-D	0	-
008 Chemical A08	-b2w	-3Dw	-w	-2w	-Dw	-3w	-B3w	-5w	-D3w	-Ddw	-w	-2w	-Dw	0	-*
009 Chemical A09	-bw	-3D	-	-w	-D	-5w	-B5w	-6w	-D5w	-Dd	-	-w	-D	0	-
010 Chemical A101	-w	-4D	-	-w	-D	-Dw	-Bw	-4w	-2Dw	-Dd	-	-w	-D	0	-
011 Chemical A102	-w	-2D	-	-w	-D	-w	-Bw	-5w	-Dw	-d	-	-w	-2D	0	-
012 Chemical A103	-w	-3Dw	-w	-w	-w	-bD2w	-X2w	-4w	-D2w	-dw	-w	-w	-w	0	-
013 Chemical A104	-D	-2D	-	-b	-	-D2w	-2w	-b4w	-2D2w	-D	-	-	-2D	0	-
Group B															
014 Chemical B01	-d	-D	-	-	-	-	-	-	-D	-d	-	-	-D	0	-
015 Chemical B101	+Bd	-D	-	-	-	-	-	-	-B?	-d	-	-	-	0	-
016 Chemical B102	-d	-D	-	-	-	-	-	-	-D	-Dd	-	-	-D	0	-
017 Chemical B103	-d	-D	-	-	-	-	-	-	-D	-	-	-	-D	0	-
018 Chemical B104	-d	-D	-	-	-	-D	-	-	-D	-D	-	-	-2D	0	-
Group C															
019 Chemical C01	-d	-2D	-b	-	-	-	-	-	-D	-D	-	-	-2D	0	-
020 Chemical C02	-d	-2D	-b	-	-	-	-	-	-D	-D	-	-	-2D	0	-
021 Chemical C03	-d	-2D	-b	-	-	-	-	-	-2D	-2D	-	-	-2D	0	-
022 Chemical C04	-d	-3D	-b	-	-	-	-	-	-2D	-Dd	-	-	-4D	0	-
023 Chemical C05	-d	-	-B?	-	-	-B	-	-	-D	-D	-B?	-	-B	4	- deg qsar
024 Chemical C06	-2d	-2D	-	-	-	-	-	-	-	-D	-	-	-3D	0	-
025 Chemical C07	-	-D	-	-	-	-	-	-	-D	-D	-	-	-	0	-
026 Chemical C08	-2w	-B?2Dw	-w	-w	-w	-w	-w	-2w	-Dw	-Dw	-w	-w	-3Dw	0	-
027 Chemical C09	-2d	-	-	-	-	-	-	-	-	-2D	-	-	-2D	0	-
028 Chemical C10	-d	-	-B?	-	-	-B	-	-	-D	-D	-B?	-	-B	4	- deg qsar
029 Chemical C11	-	-	-B?	-	-	-B	-	-	-B2D	-	-B?	-	-B	4	- deg qsar
030 Chemical C12	-	-	-	-	-	-	-	-	-B3D	-	-	-	-2D	0	-
031 Chemical C13	-	-	-	-	-	-	-	-	-B3D	-	-	-	-2D	0	-
032 Chemical C14	-	-	-	-	-	-D	-	-	-B4D	-D	-	-	-3D	0	-
033 Chemical C15	-2w	+B?w	-w	-w	-w	-w	-w	-2w	-B3Dw	-w	-w	-w	-2Dw	1	-
034 Chemical C101	-d	-	-	-	-	-	-	-	-2D	-D	-	-	-2D	0	-
035 Chemical C102	-2d	-	-	-	-	-	-	-	-D	-D	-	-	-D	0	-
036 Chemical C103	-d	-	-	-	-	-	-	-	-D	-2D	-	-	-2D	0	-
037 Chemical C104	-2d	-	-	-	-	-	-	-	-2D	-	-	-	-D	0	-
038 Chemical C105	-d	-	-	-	-	-	-	-	-D	-D	-	-	-2D	0	-
039 Chemical C106	-d	-D	-	-	-	-	-	-	-D	-D	-	-	-2D	0	-
040 Chemical C107	-2d	-D	-	-	-	-	-	-	-D	-	-	-	-D	0	-
Group D															
041 Chemical D01	+2B	-B3D	-	+2B	+B	+BB?2w	-2w	-b2w	+2B2w	-BDd	-	-B	-B3D	12	+
042 Chemical D02	-	-D	-	-	-	-4w	-4w	-6w	-D4w	-D	-	-	-D	0	-
043 Chemical D03	+B	+B	-B	-	-	-B4w	-B4w	-6w	-4w	+B	+B	-	-	7	+
044 Chemical D04	-	-D	-	-	-	-4w	-4w	-6w	-4w	-D	-	-	-	0	-
045 Chemical D05	+B	-B3D	-	+B	+B	+B2w	-2w	-2w	-BD2w	+Bd	-	-B	-B3D	9	+
046 Chemical D101	-b	-D	-	-	-	-w	-Bw	-w	-Dw	-d	-	-	-D	0	-
047 Chemical D102	-D	-	-	-	-	-D4w	-4w	-6w	-4w	-2D	-	-	-D	0	-

LEGEND TO TABLE 3

^a**MC No.:** The *MC4PC* program automatically counts and enumerates each of the test compounds being analyzed.

^b**Compound Name:** The name of the test compound being analyzed in the *MC4PC* QSAR tests.

^c**Structural Alerts / *Salmonella typhimurium* Mutagenicity Modules:** An explanation for the different codes for molecular structural alerts identified by the *MC4PC* program is provided in a glossary at the end of this report. Additional information on the individual *Salmonella typhimurium* mutagenicity database modules (**A2J, A6K-A6M, A6O, A6P, A6R, A6S, A6U-A6X, and A6Z**) is provided in **Section II.A.3**.

^d**No. SSA:** The total number of structurally similar alerts (**SSA**) identified by *MC4PC* in the test compound is used to predict the mutagenic potential of the test compound. The SSA value refers to the SSA identified using the **A2J, A6K-A6M, A6O, A6P, A6R, A6S, A6U-A6X, and A6Z** modules.

^e**Overall Call:** The expert opinion call refers to the evaluation of the activity of the test compound, including: '+', active compounds have ≥ 2 SSA; '-', inactive compounds have < 2 SSA; and '+?' for compounds that are possibly active. See the glossary at the end of this report for other codes.

Table 4: Summary of the MC4PC Estimated and Actual Adverse Liver Effects of Forty-seven (47) Compounds in Adult Humans

MC No. ^a Compound Name ^b	Structural Alerts / Adverse Liver Effects Modules ^c												Expert Opinions	
	A10 Enz.	A11 API	A12 SGOT	A13 SGPT	A15 GGTI	A16 Obst.	A17 Bili.	A18 Jaun.	A19 JC	A21 Path.	A22 Fail.	A23 Dam.	No. SSA ^d	Overall Call ^e
TEST AND MODEL COMPOUNDS														
Group A														
001 Chemical A01	-Dw	-Dw	-Ddw	-Dw	-bw	-2dw	-Ddw	-Ddw	-Ddw	-D2w	-dw	-Dw	0	-
002 Chemical A02	-dw	-w	-dw	-w	-bw	-2dw	-Ddw	-Ddw	-2Ddw	-2w	-dw	-Dw	0	-
003 Chemical A03	-D	-	-D	-D	-bD	-d	-Dd	-Dd	-2Dd	-Dw	-D2d	-D	0	-
004 Chemical A04	-Dw	-w	-Dw	-Dw	-2Dw	-dw	-Dw	-Dw	-Ddw	-Dw	-2Ddw	-Dw	0	-
005 Chemical A05	-Dw	-Dw	-Dw	-Dw	-bw	-dw	-Ddw	-Ddw	-Ddw	-D2w	-dw	-Dw	0	-
006 Chemical A06	-D2w	-D2w	-D2w	-D2w	-b2w	-d2w	-Dd2w	-Dd2w	-Dd2w	-D3w	-d2w	-D2w	0	-*
007 Chemical A07	-2Dw	-Dw	-2Dw	-2Dw	-bw	-Ddw	-Ddw	-2Ddw	-Ddw	-D2w	-Ddw	-Dw	0	-
008 Chemical A08	-2D2w	-D2w	-2D2w	-b2D2w	-2w	-Dd2w	-Dd2w	-2Dd2w	-d2w	-D3w	-Dd2w	-b2w	0	-*
009 Chemical A09	-2Dw	-Dw	-2Dw	-b2Dw	-w	-Ddw	-Ddw	-2Ddw	-dw	-D2w	-Ddw	-bw	0	-
010 Chemical A101	-Dw	-Dw	-Dw	-Dw	-bw	-dw	-Ddw	-Ddw	-Ddw	-D2w	-dw	-Dw	0	-
011 Chemical A102	-dw	-w	-dw	-w	-bw	-2dw	-Ddw	-Ddw	-2Ddw	-2w	-dw	-Dw	0	-
012 Chemical A103	-w	-w	-w	-w	-bw	-dw	-Ddw	-Ddw	-2Ddw	-2w	-dw	-Dw	0	-
013 Chemical A104	-2D	-D	-2D	-D	-2D	-D	-d	-2Dd	-D	-3D	-3D	-4D	0	-
Group B														
014 Chemical B01	+B	-B	+B	+B	-2D	+B?	-Bd	-b	-B?	-B?	-B?	-b	8	+
015 Chemical B101	+B	-D	+B	+B	-D	-d	-D	-D	-D	-	-	-bD	3	+
016 Chemical B102	-2D	-2D	-D	-	-2D	-B?D	-Dd	-D	-	-	-	-b	0	-
017 Chemical B103	-D	-D	-D	-	-D	-D	-d	-D	-	-	-	-	0	-
018 Chemical B104	-D	-D	-D	-	-2D	-D	-d	-D	-	-D	-D	-	0	-
Group C														
019 Chemical C01	-D	-4D	-D	-D	-4D	-2D	-3Dd	-D	-2D	-2D	-D	-3D	0	-
020 Chemical C02	-D	-5D	-D	-D	-4D	-2D	-Dd	-	-D	-D	-D	-3D	0	-
021 Chemical C03	-D	-5D	-D	-D	-4D	-2D	-Dd	-d	-2D	-D	-2D	-3D	0	-
022 Chemical C04	-D	-4D	-D	-D	-4Dd	-2D	-2Dd	-	-2D	-2D	-D	-3D	0	-
023 Chemical C05	-Dw	-3D	-D	-D	-3Dw	-3Dw	-D2d	-	-Dw	-Dw	-Dw	-2D	0	-
024 Chemical C06	-D	-2D	-D	-Dd	-2D	-Dd	-2d	-	-2D	-D	-D	-2D	0	-
025 Chemical C07	-	-2D	-	-d	-2D	-	-	-	-D	-D	-	-D	0	-
026 Chemical C08	-bDw	-4Dw	-Dw	-Ddw	-3Dw	-2Dw	-Ddw	-w	-Dw	-w	-Dw	-Dw	0	-
027 Chemical C09	-D	-D	-D	-D	-D	-2D	-2d	-D	-2D	-	-D	-	0	-
028 Chemical C10	-Dw	-3D	-D	-D	-3Dw	-3Dw	-D2d	-d	-Dw	-2Dw	-Dw	-2D	0	-
029 Chemical C11	-Dw	-2D	-D	-	-2Dw	-2Dw	-2d	-d	-2Dw	-Dw	-w	-D	0	-
030 Chemical C12	-D	-2D	-D	-	-2D	-2D	-2d	-	-2D	-	-	-	0	-
031 Chemical C13	-D	-2D	-D	-	-2D	-2D	-d	-	-2D	-	-	-	0	-
032 Chemical C14	-Dw	-2Dw	-Dw	-w	-2Dw	-2Dw	-dw	-w	-2Dw	-w	-w	-w	0	-
033 Chemical C15	-bDw	-2Dw	-Dw	-w	-2Dw	-2Dw	-dw	-w	-2Dw	-w	-w	-w	0	-
034 Chemical C101	-D	-3D	-D	-D	-3D	-3D	-D2d	-	-D	-D	-D	-D	0	-
035 Chemical C102	-DI	-2DI	-DI	-DI	-2DI	-2DI	-2DI	-DI	-DI	-I	-I	-I	0	-I
036 Chemical C103	-DI	-3DI	-DI	-DI	-3DI	-3DI	-D2dI	-DI	-DI	-DI	-DI	-DI	0	-I
037 Chemical C104	-D	-2D	-D	-D	-2D	-2D	-2d	-	-D	-	-	-	0	-
038 Chemical C105	-D	-3D	-D	-D	-3D	-3D	-D2d	-	-D	-D	-D	-D	0	-
039 Chemical C106	-D	-4D	-D	-Dd	-4D	-2D	-Dd	-	-D	-D	-D	-2D	0	-
040 Chemical C107	-D	-3D	-D	-Dd	-3D	-D	-d	-	-D	-	-	-D	0	-
Group D														
041 Chemical D01	-Dd	-D	-2Dd	-d	+B	+B	-	+B	+B	+B	+B	-Dd	5	+
042 Chemical D02	-Dd	-D	-D	-	-D	-D	-d	-2d	-D	-D	-D	-D	0	-
043 Chemical D03	-Dd	-	-D	-	-	-	-d	-2d	-D	-D	-D	-D	0	-
044 Chemical D04	-Dd	-	-D	-	-	-	-d	-2d	-D	-D	-D	-D	0	-
045 Chemical D05	-Dd	-B2D	-2Dd	-	+B	+B	-	+B	+2B	+B	-3D	-D	7	+
046 Chemical D101	-2d	-2D	-	-	-D	-	-d	-D	-4D	-D	-2D	-D	0	-
047 Chemical D102	-I	-dI	-I	-I	-DI	-I	-dI	-2dI	-DI	-DI	-DI	-DI	0	-I

LEGEND TO TABLE 4

^a**MC No.:** The *MC4PC* program automatically counts and enumerates each of the test compounds being analyzed.

^b**Compound Name:** The name of the test compound being analyzed in the *MC4PC* QSAR tests.

^c**Structural Alerts / Adverse Liver Effects Modules:** An explanation for the different codes for molecular structural alerts identified by the *MCASE* program is provided in a glossary at the end of this report. Additional information on the adverse liver effects database modules (**A10-A13**, **A15-A19**, and **A21-A23**) is provided in **Section II.B.1**. In Table 6, structural alerts are pooled separately for three independent groups of modules: 1) **A10-A13**, and **A15** (liver enzyme endpoints); 2) **A16-A19** (liver obstruction endpoints); and 3) **A21-A23** (liver pathology endpoints).

^d**No. SSA:** The total number of structurally similar alerts (**SSA**) identified by *MCASE* in the test compound is used to predict the adverse liver effects potential of the test compound.

The SSA value refers to the SSA identified using the three groups of modules: 1) **A10-A13**, and **A15**; 2) **A16-A19**; and 3) **A21-A23**.

^e**Overall Call:** The expert opinion call refers to the evaluation of the activity of the test compound, including: '+', active compounds have ≥ 2 SSA; '-', inactive compounds have < 2 SSA; and '+?' for compounds that are possibly active. See the glossary at the end of this report for other codes.

Table 5: Summary of the MC4PC Estimated and Actual Adverse Immunological Effects of Forty-seven (47) Compounds in Adult Humans

MC No. ^a Compound Name ^b	Structural Alerts / Adverse Immunological Effects Modules ^c												Expert Opinions	
	A30 Marr.	A31 Leuk.	A32 Panc.	A40 Agr.	A41 Depr.	A42 Eos.	A33 Skin	A34 Rash	A35 Prur.	A36 Urt.	A37 Alle.	A38 Edema	No. SSA ^d	Overall Call ^e
TEST AND MODEL COMPOUNDS														
Group A														
001 Chemical A01	-w	-w	-w	-Dw	-2Dw	-2D2w	+Bw	-B	-B?2w	-d2w	-w	+Bd2w	1	-
002 Chemical A02	-w	-w	-w	-Dw	-Dw	-2D2w	+Bw	-B	-B?2w	-d2w	-w	+Bd2w	1	-
003 Chemical A03	-d	-B?d	-D	-2D	-2D	-2Dw	+B	-	+B?w	+B?dw	-	+Bdw	1	-
004 Chemical A04	-dw	-bdw	-Dw	-2Dw	-2Dw	-2Dw	-w	-w	+B?w	-w	-bw	+Bw	1	-
005 Chemical A05	-w	-w	-w	-Dw	-Dw	-2D2w	+Bw	-	+B?2w	-d2w	-w	+Bd2w	1	-
006 Chemical A06	-2w	-2w	-2w	-D2w	-2D2w	-2D3w	+B2w	+Bw	+B?3w	-d3w	-2w	+Bd3w	1	-*
007 Chemical A07	-dw	-w	-w	-2Dw	-3Dw	-2D2w	+Bw	-	+B?2w	-d2w	-w	+Bd2w	1	-
008 Chemical A08	-b2w	-2w	-2w	-2D2w	-3D2w	-2D3w	-X?2w	+BB?w	-b3w	-bd3w	-2w	+Bd3w	1	-*
009 Chemical A09	-dw	-w	-w	-2Dw	-3Dw	-2D2w	-X?w	+B?	-b2w	-bd2w	-w	+Bd2w	1	-
010 Chemical A101	-w	-w	-w	-Dw	-2Dw	-2D2w	+Bw	-	-B?2w	-d2w	-w	+Bd2w	1	-
011 Chemical A102	-w	-w	-w	-Dw	-Dw	-2D2w	+Bw	-B	-B?2w	-d2w	-w	+Bd2w	1	-
012 Chemical A103	-w	-w	-w	-Dw	-Dw	-2D2w	+Bw	-w	+B?2w	-d2w	-w	+Bd2w	1	-
013 Chemical A104	-d	-d	-Dd	-2D	-Dd	-Dd	+B	+BB?	+Bb	+B	-b	+B	3	+
Group B														
014 Chemical B01	-	-B	-d	-Dd	-	-D	-b	+2BB?	+B?	-B	+BB?	-B	5	+
015 Chemical B101	-	-	-	-d	-	-	-	+Bb	-	-	+Bd	-	1	-
016 Chemical B102	-	-Bb	-d	-D	-	-3D	-b	+2B	+BB?	-B	+BB?	-B	5	+
017 Chemical B103	-	-	-	-D	-	-D	-	+2B	-	-	+B	-	1	-
018 Chemical B104	-Dd	-d	-D	-2D	-	-D	-	-B	-	-	+B	-	1	-
Group C														
019 Chemical C01	-D	-d	-D	-Dd	-bD	-D	-bD	-	-bD	-D	-D	-d	0	-
020 Chemical C02	-D	-d	-D	-2D	-2D	-2D	-D	-	-BB?D	-D	-D	-d	1	-
021 Chemical C03	-D	-d	-D	-2D	-2D	-D	-D	-	-B?D	-D	-D	-2d	0	-
022 Chemical C04	-2D	-d	-D	-2Dd	-2D	-D	-D	-	-bD	-D	-b2D	-d	0	-
023 Chemical C05	-Dw	-d	-Ddw	-Dw	-Ddw	-2D	-bD	-	-D	-D	-Dd	-d	0	-
024 Chemical C06	-	-d	-D	-Dd	-2D	-D	-	-B	-B	-	+Bd	-2d	1	-
025 Chemical C07	-	+Bd	-	-D	-	-	-	-B?	-	-	-	-	1	-
026 Chemical C08	-w	-dw	-Dw	-2Dw	-Ddw	-w	-w	-Bw	-Bw	-w	-w	-dw	1	-
027 Chemical C09	-	-	-D	-d	-D	-D	-	-B	-	-	+B	-d	1	-
028 Chemical C10	-Dw	-d	-Ddw	-Dw	-Ddw	-D	-D	-	-D	-D	-D	-d	0	-
029 Chemical C11	-2Dw	-	-Ddw	-Dw	-dw	-2D	-	-	-b	-b	-D	-	0	-
030 Chemical C12	-2D	-	-D	-D	-	-2D	-	-	-b	-b	-D	-	0	-
031 Chemical C13	-2D	-	-D	-D	-	-D	-	-	+Bb	-b	-D	-	1	-
032 Chemical C14	-2Dw	-w	-Dw	-Dw	-w	-Dw	-w	-w	-bw	-bw	-Dw	-w	0	-
033 Chemical C15	-2Dw	-w	-Dw	-Dw	-w	-Dw	-w	-w	-bw	-bw	-Dw	-w	0	-
034 Chemical C101	-D	-d	-D	-D	-D	-D	-D	-	-D	-D	-D	-d	0	-
035 Chemical C102	-I	+BI	-DI	-DI	-I	-2DI	-I	-I	-I	-I	-dI	-I	1	-I
036 Chemical C103	-DI	-dI	-DI	-DI	-DI	-DI	-DI	+BI	-DI	-DI	-DI	-dI	1	-I
037 Chemical C104	-	-	-D	-D	-	-2D	-	-	-	-	-d	-	0	-
038 Chemical C105	-D	-d	-D	-D	-D	-D	-D	-	-D	-D	-D	-d	0	-
039 Chemical C106	-D	+B2d	-D	-D	-D	-D	-D	-	-D	-D	-D	-d	1	-
040 Chemical C107	-	+Bd	-D	-D	-	-2D	-	-	-	-	-	-	1	-
Group D														
041 Chemical D01	-2d	+B?	-D	-Dd	-4D	-Dd	+Bd	-	-	-	-	+B	2	+
042 Chemical D02	-2D	-	-D	-2D	-D	-d	-b	+B	+B	-d	-D	-d	1	-
043 Chemical D03	-D	-	-D	-D	-D	-d	-b	+B	-	-d	-D	-d	1	-
044 Chemical D04	-D	-	-D	-D	-D	-d	-b	+B	+B	-d	-D	-d	1	-
045 Chemical D05	-2d	+B?	-2D	-2Dd	-5D	-Dd	+Bd	-b	-	-	-	+B	2	+
046 Chemical D101	-D	-	-d	-D	-2D	-d	-	+B	+Bb	-	-	-bd	1	-
047 Chemical D102	-dI	+B?A	-DI	-DI	-DI	-dI	-I	-M	-I	-dI	-I	-dI	1	-A

LEGEND TO TABLE 5

^a**MC No.:** The *MC4PC* program automatically counts and enumerates each of the test compounds being analyzed.

^b**Compound Name:** The name of the test compound being analyzed in the *MC4PC* QSAR tests.

^c**Structural Alerts / Adverse Immunological Effects Module:** An explanation for the different codes for molecular structural alerts identified by the *MC4PC* system is provided in a glossary at the end of this report. Additional information on the adverse immunological effects database modules (**A29**, **A30-A38** and **A40-A42**) is provided in **Section II.B.2**.

^d**No. SSA:** The total number of structurally similar alerts (**SSA**) identified by *MC4PC* in the test compound is used to predict the adverse immunological effects potential of the test compound. The SSA value refers to the SSA identified across modules **A30-A38** and **A40-A42**.

^e**Overall Call:** The expert opinion call refers to the evaluation of the activity of the test compound, including: '+', active compounds have ≥ 2 SSA; '-', inactive compounds have < 2 SSA; and '+?' for compounds that are possibly active. See the glossary at the end of this report for other codes.

Table 6: Summary of the MC4PC Estimated and Actual Adverse Kidney Effects of Forty-seven (47) Compounds in Adult Humans

MC No. ^a Compound Name ^b	Structural Alerts / Adverse Kidney Effects Modules ^c												Expert Opinions	
	A1H Urin.	A1I Ret.	A1J Inco.	A1K Freq.	A1L Dys.	A1A Kidn.	A1B Ac.F.	A1C Fail.	A1D Hema.	A1E BUN	A1F Crea.	A1G Func.	No. SSA ^d	Overall Call ^e
TEST AND MODEL COMPOUNDS														
Group A														
001 Chemical A01	-2w	-2D2w	-2D2w	-2D2w	-2w	-2d2w	-d2w	-D2w	-2D3d2w	-B2w	-Ddw	-B2w	2	-* qsar
002 Chemical A02	-2w	-2D2w	-2D2w	-2D2w	-2w	-2d2w	-d2w	-D2w	-2D2d2w	-B2w	-Ddw	-B2w	2	-* qsar
003 Chemical A03	-w	-2Dw	-4Dw	-2Dw	-Dw	-2dw	-Ddw	-Ddw	-2D3dw	+Bw	-Dd	+Bw	2	+
004 Chemical A04	-w	-2Dw	-2Dw	-Dw	-dw	-dw	-bDdw	-Ddw	-2D2dw	-Bw	-Dw	-Bw	2	- qsar
005 Chemical A05	-B2w	-2D2w	-2D2w	-2D2w	-B2w	-2d2w	-d2w	-D2w	-2D2d2w	+B2w	-Ddw	+B2w	4	+
006 Chemical A06	-3w	-2D3w	-2D3w	-2D3w	-3w	-2d3w	-d3w	-D3w	-2D2d3w	-B3w	-Dd2w	-B3w	2	-* qsar
007 Chemical A07	-2w	-2D2w	-2D2w	-2D2w	-2w	-2d2w	-d2w	-D2w	-3D2d2w	-B2w	-Ddw	-B2w	2	-* qsar
008 Chemical A08	-3w	-2D3w	-2D3w	-bD3w	-3w	-2d3w	-d3w	-D3w	-2D3d3w	+B3w	-Dd2w	+B3w	2	-*
009 Chemical A09	-2w	-2D2w	-2D2w	-bD2w	-2w	-2d2w	-d2w	-D2w	-2D2d2w	-B2w	-Ddw	-B2w	2	-* qsar
010 Chemical A101	-2w	-2D2w	-2D2w	-2D2w	-d2w	-2d2w	-d2w	-D2w	-2D3d2w	+B2w	-Ddw	+B2w	2	+
011 Chemical A102	-2w	-2D2w	-2D2w	-2D2w	-2w	-2d2w	-d2w	-D2w	-2D2d2w	-B2w	-Ddw	-B2w	2	-* qsar
012 Chemical A103	-2w	-2D2w	-2D2w	-2D2w	-d2w	-2d2w	-d2w	-D2w	-2Dd2w	+B2w	-Ddw	+B2w	2	+
013 Chemical A104	-3D	-4D	-4D	-D	-2D	-d	-D	-d	-D2d	+B	-2d	-B	2	+? qsar
Group B														
014 Chemical B01	-D	-D	-D	-	-D	+B?	-	-	-	-D	-D	-bD	1	-
015 Chemical B101	-2Dd	-2D	-2D	-	-	-	-	-	-D	-D	-D	-D	0	-
016 Chemical B102	-D	-Dd	-2D	-	-2D	+2B?	-	-d	-Dd	-D	+B	-bD	2	+?
017 Chemical B103	-	-	-	-	-	-	-	-	-	-D	-	-D	0	-
018 Chemical B104	-	-D	-	-	-	-	-D	-d	-	-D	-Dd	-2D	0	-
Group C														
019 Chemical C01	-Dd	-D	-2D	-D	-D	-D	-d	-D	-D	-	-D	-d	0	-
020 Chemical C02	-D	-2D	-3D	-3D	-d	-D	-bd	-D	-	-	-D	-d	0	-
021 Chemical C03	-D	-D	-3D	-2D	-	-D	-bd	-D	-	-	-D	-d	0	-
022 Chemical C04	-D	-D	-2D	-D	-	-D	-d	-D	-Dd	-	-D	-d	0	-
023 Chemical C05	-Ddw	-2d	-2Dw	-w	-d	-D	-d	-Dw	-d	-D	-2D	-2d	0	-
024 Chemical C06	-D	-d	-2D	-2D	-	-D	-d	-2D	-	-3D	-Dd	-Dd	0	-
025 Chemical C07	-D	-d	-2D	-D	-	-	-	-	-	-D	-	-	0	-
026 Chemical C08	-Dw	-dw	-2Dw	-Dw	-w	-Dw	-dw	-Dw	-w	-2Dw	-Dw	-dw	0	-
027 Chemical C09	-2D	-	-2D	-2D	-	-D	-d	-2D	-d	-2D	-2D	-Dd	0	-
028 Chemical C10	-Ddw	-d	-2Dw	-Dw	-2d	-D	-d	-Dw	-d	-D	-2D	-2d	0	-
029 Chemical C11	-D2dw	-Dd	-3Dw	-Dw	-2d	-	-	-w	-d	-D	-D	-d	0	-
030 Chemical C12	-2Dd	-D	-3D	-D	-	-	-	-	-d	-D	-Dd	-	0	-
031 Chemical C13	-2Dd	-D	-3D	-D	-	-	-	-	-d	-D	-BDd	-	0	-
032 Chemical C14	-2Ddw	-Dw	-3Dw	-Dw	-w	-w	-w	-w	-dw	-Dw	-Ddw	-w	0	-
033 Chemical C15	-2Ddw	-Dw	-3Dw	-Dw	-w	-w	-w	-w	-dw	-Dw	-Ddw	-w	0	-
034 Chemical C101	-2D	-	-2D	-D	-	-D	-d	-D	-d	-D	-2D	-d	0	-
035 Chemical C102	-2DI	-dl	-2DI	-DI	-dl	-DI	-l	-DI	-Ddl	-DI	-2DI	-l	0	-l
036 Chemical C103	-2DI	-l	-2DI	-DI	-l	-DI	-dl	-DI	-dl	-DI	-2DI	-dl	0	-l
037 Chemical C104	-2D	-d	-2D	-D	-d	-D	-	-D	-Dd	-D	-2D	-	0	-
038 Chemical C105	-2D	-	-2D	-D	-	-B?D	-d	-D	-d	-D	-2D	-d	0	-
039 Chemical C106	-D	-d	-2D	-D	-	-D	-d	-D	-	-D	-D	-d	0	-
040 Chemical C107	-D	-d	-2D	-D	-d	-D	-	-D	-D	-D	-D	-	0	-
Group D														
041 Chemical D01	-D	-	-3D	-3D	-D	-	-2D	-2D	-	-2D	-d	-2D	0	-
042 Chemical D02	-d	-	-D	-2D	-D	-2d	-D	-D	-D	-D	+Bb2d	-D	1	-
043 Chemical D03	-d	-d	-D	-2D	-D	-2d	-D	-D	-D	-D	-bd	-D	0	-
044 Chemical D04	-d	-	-D	-2D	-D	-2d	-D	-D	-D	-D	+Bbd	-D	1	-
045 Chemical D05	-D	-	-3D	-2D	-2D	-	-3D	-D	-	-2D	-d	-3D	0	-
046 Chemical D101	-	-	-D	-3D	-D	-d	-D	-D	-	-D	-	-2D	0	-
047 Chemical D102	-l	-dl	-DI	-2DI	-DI	-dl	-DI	-DI	-DI	-l	-dl	-DI	0	-l

LEGEND TO TABLE 6

^a**MC No.:** The *MC4PC* program automatically counts and enumerates each of the test compounds being analyzed.

^b**Compound Name:** The name of the test compound being analyzed in the *MC4PC* QSAR tests.

^c**Structural Alerts / Adverse Kidney Effects Module:** An explanation for the different codes for molecular structural alerts identified by the *MC4PC* program is provided in a glossary at the end of this report. Additional information on the adverse kidney effects database modules (**A1A-A1L**) is provided in **Section II.B.3**. In Table 6, structural alerts are pooled separately for the two independent groups of modules: 1) **A1H-A1L** (urinary tract endpoints); and 2) **A1A-A1G** (kidney function endpoints).

^d**No. SSA:** The total number of structurally similar alerts (**SSA**) identified by *MC4PC* in the test compound is used to predict the adverse kidney effects potential of the test compound. The SSA value refers to the SSA identified using the two groups of modules: 1) **A1H-A1L**; and 2) **A1A-A1G**.

^e**Overall Call:** The expert opinion call refers to the evaluation of the activity of the test compound, including: '+', active compounds have ≥ 2 SSA; '-', inactive compounds have < 2 SSA; and '+?' for compounds that are possibly active. See the glossary at the end of this report for other codes.

Table 7: Summary of the MC4PC Estimated and Actual Adverse Cardiological Effects of Forty-seven (47) Compounds in Adult Humans

MC No. ^a	Compound Name ^b	Structural Alerts / Adverse Cardiological Effects Modules ^c														Expert Opinions	
		AI1 Path.	AI2 Arre.	AI3 Fail.	AI8 Tach.	AJ1 Palp.	AJ2 Arrh.	AJ5 Comb.	AJ6 Hypo.	AJ7 Vaso.	AJ8 Shock	AJ9 Sync.	AI5 Circ.	AI6 Inf.	AK1 CA	No. SSA ^d	Overall Call ^e
TEST AND MODEL COMPOUNDS																	
Group A																	
001	Chemical A01	-Dd2w	-Dd2w	-2w	-w	-X?w	-w	-X?w	-B2w	-2dw	-d2w	+B2w	-2D2w	-Dd2w	-2D2w	4	+?* qsar
002	Chemical A02	-Dd2w	-Dd2w	-2w	-w	-X?w	-w	-X?w	+B2w	-2dw	-d2w	+B2w	-2D2w	-Dd2w	-2D2w	4	+*
003	Chemical A03	-bD2dw	-D2dw	-Ddw	+B	-D	-BD	-D	-Bw	+B	-2dw	+Bw	-4Dw	-Ddw	-4Dw	5	+
004	Chemical A04	-D2dw	-D2dw	-Dw	-Dw	-Dw	-Dw	-Dw	-Bw	-D2dw	-dw	+Bw	-3Dw	-Dw	-3Dw	2	+? qsar
005	Chemical A05	-B?Dd2w	-Dd2w	-2w	-bw	-X?w	-dw	-X?w	+B2w	-2dw	-d2w	+B2w	-2D2w	-Dd2w	-2D2w	4	+*
006	Chemical A06	-Dd3w	-Dd3w	-3w	-2w	-X?2w	-2w	-X?2w	+B3w	-2d2w	-d3w	+B3w	-2D3w	-Dd3w	-2D3w	4	+*
007	Chemical A07	-Dd2w	-Dd2w	-2w	-w	-X?w	-w	-X?w	+B2w	-2dw	-d2w	+B2w	-3D2w	-Dd2w	-3D2w	4	+*
008	Chemical A08	-Dd3w	-D3w	-3w	-2w	-X?2w	-2w	+B2w	+B3w	-2d2w	-d3w	+B3w	-3D3w	-Dd3w	-2D3w	2	+*
009	Chemical A09	-Dd2w	-D2w	-2w	-w	-X?w	-w	-X?w	+B2w	-2dw	-d2w	+B2w	-3D2w	-Dd2w	-3D2w	4	+*
010	Chemical A101	-Dd2w	-Dd2w	-2w	-w	-X?w	-w	-X?w	+B2w	-2dw	-d2w	+B2w	-2D2w	-Dd2w	-2D2w	4	+*
011	Chemical A102	-Dd2w	-Dd2w	-2w	-w	-X?w	-w	-X?w	+B2w	-2dw	-d2w	+B2w	-2D2w	-Dd2w	-2D2w	4	+*
012	Chemical A103	-Dd2w	-Dd2w	-2w	-w	-w	-w	+B2w	+B2w	-2dw	-d2w	+Bb2w	-2D2w	-Dd2w	-2D2w	2	+*
013	Chemical A104	-d	-d	-D	-D	-Dd	-2D	-bD	-B2d	-Dd	-bD2d	+Bbd	-D	-Dd	-b2D	2	+? de
Group B																	
014	Chemical B01	-	-	-	-	-	-D	-	-	-B?b	-	-b	-D	-	-Dd	0	-
015	Chemical B101	-	-	-	-	-b	-D	-	+B	-B?	-d	-b	-D	-	-D	1	-
016	Chemical B102	-d	-	-	-	+B	-BD	+B	-	-B	+B	-Bb	-	+B	-Dd	7	+
017	Chemical B103	-d	-	-	-	-	-	-	-	-	-	-b	-	-	-	0	-
018	Chemical B104	-d	-d	-D	-D	-D	-D	-D	-	-D	-d	-b	-2D	-	-2D	0	-
Group C																	
019	Chemical C01	-2Dd	-D	-Dd	-	-d	-D	-	-	-Dd	-2d	-	-2D	-Dd	-D	0	-
020	Chemical C02	-2Dd	-D	-Dd	-	-	-D	-	-	-D	-2d	-	-D	-Dd	-	0	-
021	Chemical C03	-2Dd	-D	-Dd	-d	-	-D	-	-	-Dd	-2d	-	-D	-Dd	-	0	-
022	Chemical C04	-2Dd	-D	-Dd	-	-	-Dd	-	-d	-D	-2d	-	-D	-Dd	-	0	-
023	Chemical C05	-D	-D	-d	-	-	-bD	-	-	-D	-d	-	-D	-D	-d	0	-
024	Chemical C06	-3Dd	-D	-2D3d	-d	-d	-D	-	-	-D	-3d	-	-Dd	-bD2d	-D	0	-
025	Chemical C07	-Dd	-	-D2d	-	-b	-D	-	-	-	-3d	-	-	-d	-	0	-
026	Chemical C08	-2Ddw	-Dw	-D3dw	-dw	-dw	-Dw	-w	-dw	-Dw	-3dw	-w	-Dw	-bD2dw	-w	0	-
027	Chemical C09	-2D	-D	-Dd	-	-	-D	-	-	-D	-d	-	-Dd	-D	-Dd	0	-
028	Chemical C10	-D	-D	-d	-	-	-D	-	-	-D	-d	-	-D	-D	-d	0	-
029	Chemical C11	-	-	-	-	-b	-D	-	-b	-	-B?d	-	-	-	-Dd	0	-
030	Chemical C12	-	-	-	-	-b	-D	-	-b	-	-B?d	-	-	-	-Dd	0	-
031	Chemical C13	-	-	-	-	+Bb	-D	-	-b	-	-B?d	-	-	-	-Dd	1	-
032	Chemical C14	-w	-w	-w	-w	-bw	-Dw	-w	-bw	-w	+B?dw	-w	-w	-w	-Ddw	1	-
033	Chemical C15	-w	-w	-w	-w	-bw	-Dw	-w	-bw	-w	-B?dw	-w	-w	-w	-Ddw	0	-
034	Chemical C101	-D	-D	-d	-	-	-D	-	-	-D	-d	-	-D	-D	-d	0	-
035	Chemical C102	-DI	-I	-I	-I	-I	-DI	-I	-I	-I	-dI	-I	-DI	-DI	-dI	0	-I
036	Chemical C103	-DI	-DI	-dI	-I	-I	-DI	-I	-I	-DI	-dI	-I	-DI	-DI	-dI	0	-I
037	Chemical C104	-D	-	-	-	-	-D	-	-	-	-d	-	-D	-D	-d	0	-
038	Chemical C105	-D	-D	-d	-	-	-D	-	-	-bD	-d	-	-D	-D	-d	0	-
039	Chemical C106	-2Dd	-D	-D3d	-	-	-D	-	-	-D	-3d	-	-D	-Dd	-	0	-
040	Chemical C107	-2Dd	-	-D2d	-	-	-D	-	-	-	-3d	-	-D	-Dd	-	0	-
Group D																	
041	Chemical D01	-Dd	-	-Dd	+BB?	-2d	-D	+BB?d	-2d	-D2d	-	+B?2d	-Dd	-D	-Dd	1	-
042	Chemical D02	-D	-	-D	+2B	-Bd	-d	-B	-d	-D	-d	-B	-D	-Dd	-D	3	+? qsar
043	Chemical D03	-D	-	-D	+2B	-d	-d	-B	-d	-D	-d	-B	-D	-Dd	-D	3	+? qsar
044	Chemical D04	-D	-	-D	+2B	-Bd	-d	-B	-d	-D	-d	-B	-D	-Dd	-D	3	+? qsar
045	Chemical D05	-Dd	-	-D	+B	-2d	-Dd	+BB?d	-2d	-Dd	-d	+B?d	-Dd	-D	-Dd	1	-
046	Chemical D101	-D	-	-2D	+2B	-d	-	-2Bb	-d	-D	-	-	-bD	-D	-D	1	-
047	Chemical D102	-dI	-I	-DI	+3BA	-DdI	-DdI	+BB?bM	-I	-DI	-dI	-BI	-I	-dI	-I	3	+?A qsar

LEGEND TO TABLE 7

^a**MC No.:** The *MC4PC* program automatically counts and enumerates each of the test compounds being analyzed.

^b**Compound Name:** The name of the test compound being analyzed in the *MC4PC* QSAR tests.

^c**Structural Alerts / Adverse Cardiological Effects Module:** An explanation for the different codes for molecular structural alerts identified by the *MC4PC* program is provided in a glossary at the end of this report. Additional information on the adverse cardiological effects database modules (**AI1-AI3**, **AI5**, **AI6**, **AI8**, **AJ1**, **AJ2**, **AJ5-AJ9**, and **AK1**) is provided in **Section II.B.4**. In Table 7, structural alerts are pooled separately for the four independent groups of modules: 1) **AI1-AI3** (heart pathology endpoints); 2) **AI8**, **AJ1**, **AJ2** (heart conduction endpoints); 3) **AJ5-AJ9** (hypotension and related endpoints); and 4) **AI5**, **AI6**, **AK1** (abnormal circulation endpoints).

^d**No. SSA:** The total number of structurally similar alerts (**SSA**) identified by *MC4PC* in the test compound is used to predict the adverse cardiological effect potential of the test compound. The SSA value refers to the SSA identified across all 14 modules.

^e**Overall Call:** The expert opinion call refers to the evaluation of the activity of the test compound, including: '+', active compounds have ≥ 2 SSA; '-', inactive compounds have < 2 SSA; and '+?' for compounds that are possibly active. See the glossary at the end of this report for other codes.

Table 8: Summary of the MCASE Estimated and Actual Experimental Maximum Tolerated Dose (MTD) Values of Forty-seven (47) Compounds in Rats and Mice

MC No. ^a	Rats or Mice Compound Name ^b	Maximum Tolerated Dose (MTD) Values in (mg/kg-bw/day) ^c								Expert Opinions Overall Call ^f
		A81		A82		A77		A78		
		A83 Act. ^d	Alerts ^e	A84 Act. ^d	Alerts ^e	A79 Act. ^d	Alerts ^e	A80 Act. ^d	Alerts ^e	
Rat MTDs										
TEST AND MODEL COMPOUNDS										
Group A										
001	Chemical A01	-	-b	-	-bD	170	+B	150	+Bb	160
002	Chemical A02	-	-b	-	-bD	174	+B	135	+Bb	150
003	Chemical A03	-	-b	-	-bD	163	+B	150	+BB?b	160
004	Chemical A04	0.000500	+B3bw	12.9	-B2bD	163	+Bbw	113 or 450	+2Bbw	140
005	Chemical A05	-	-b	-	-bD	163	+Bb	7.00	+B2b	85
006	Chemical A06	-	-bw	-	-bDw	517	+Bw	-	+Bbw	520
007	Chemical A07	25.0	+B2b	24.8	-B2bD	517	+B	619	+Bb	520
008	Chemical A08	19.9	+B?2bw	-	-2bDw	426	+Bdw	254	+Bbdw	340
009	Chemical A09	19.9	+BB?2b	24.8	-B2bD	517	+Bd	250	+Bb	250
010	Chemical A101	-	-b	-	-bD	163	+B	135	+Bb	150
011	Chemical A102	-	-b	-	-bD	174	+B	135	+Bb	150
012	Chemical A103	-	-b	-	-bD	152	+B	135	+B	94
013	Chemical A104	-	-4bD	-	-2bD	174	-b	8.00	-Bb	8.0
Group B										
014	Chemical B01	-	-d	-	-d	210	+B2b	100	+B?b	160
015	Chemical B101	-	-	42.0	+Bb	174	-3b	150	+Bb	96
016	Chemical B102	-	-bd	-	-bd	125	+BB?b	152	+B?b	130
017	Chemical B103	-	-	-	-	-	-b	-	-b	70
018	Chemical B104	-	-b	-	-	2500	+B2b	450	+B2b	1500
Group C										
019	Chemical C01	-	-b	-	-	-	-	750	+B	750
020	Chemical C02	-	-bD	-	-D	3.30	-B2b	75.0	-Bb	39
021	Chemical C03	-	-bD	-	-D	152	+B2b	62.0	-B2b	150
022	Chemical C04	-	-b	-	-	-	-	19.4	-B	19
023	Chemical C05	-	-D	-	-D	174	+Bb	508	+Bb	340
024	Chemical C06	-	-b	-	-b	-	-	-	-bd	70
025	Chemical C07	0.673	+Bb	-	-	-	-	-	-	0.67
026	Chemical C08	-	-bw	-	-bw	-	-w	-	-3bdw	70
027	Chemical C09	-	-	-	-	-	-	-	-d	70
028	Chemical C10	-	-	-	-	-	-	-	-	70
029	Chemical C11	25.0	+BB?	8.21	+BB?	-	-	-	-	17
030	Chemical C12	25.0	+BB?	3.97	+BB?	-	-	-	-	14
031	Chemical C13	25.0	+BB?b	3.97	+BB?	-	-	-	-	14
032	Chemical C14	25.0	+BB?b2w	5.39	+BB?2w	-	-2w	-	-2w	15*
033	Chemical C15	-	-	-	-b	-	-	-	-b	70
034	Chemical C101	-	-	-	-	-	-	-	-	70
035	Chemical C102	-	-	-	-	-	-	-	-	70 (50 Expt.)
036	Chemical C103	-	-	-	-	-	-	-	-	70
037	Chemical C104	-	-	-	-	-	-	-	-	70
038	Chemical C105	-	-w	-	-w	-	-w	-	-w	70
039	Chemical C106	-	-	-	-	-	-	-	-	70
040	Chemical C107	-	-	-	-	-	-	-	-	70
Group D										
041	Chemical D01	-	-b	-	-bD	152	+B	100	+B	130
042	Chemical D02	-	-b	-	-	-	-d	-	-d	70
043	Chemical D03	-	-	-	-	-	-bd	-	-bd	70
044	Chemical D04	-	-	-	-	-	-d	-	-d	70
045	Chemical D05	-	-2b	-	-2bD	152	+B	100	+B	130
046	Chemical D101	-	-	-	-	-	-	-	-b	70
047	Chemical D102	29.8	+Bb	23.1	+B	-	-d	-	-bd	26 (25 Expt.)

**Mouse MTDs
TEST AND MODEL COMPOUNDS**

Group A

001 Chemical A01	32.0	+B2b	-	-b2w	-	-	-	-b2w	32
002 Chemical A02	32.0	+B2b	-	-b2w	500	+B	450	+B2b2w	450
003 Chemical A03	32.0	+B2b	-	-b	541	+B2b	400 or 575	+2Bb	470
004 Chemical A04	32.0	+B2bw	11.0	+B2bw	541	+B2b	257or 575	+2Bb	260
005 Chemical A05	32.0	+B3b	-	-b	-	-	-	-b	32
006 Chemical A06	32.0	+B2bw	-	-bw	-	-w	-	-bdw	32
007 Chemical A07	32.0	+B3b	-	-b	-	-	202	+Bbd	120
008 Chemical A08	80.0	+B3bw	-	-2bw	300	+B?bw	-	-dw	80
009 Chemical A09	80.0	+B4b	-	-b	32300	+B?bw	202	+Bd	140
010 Chemical A101	32.0	+B2b	-	-b	-	-	-	-b	32
011 Chemical A102	32.0	+B2b	-	-b2w	500	+B	450	+B2b2w	450
012 Chemical A103	0.00200	+B2bw	-	-bw	-	-w	1050	+B2bw	0.0020 [†]
013 Chemical A104	7.70	+B2b	13.7	+B	500 or 500	+2Bb	603	+B	500

Group B

014 Chemical B01	-	-D	-	-D	32300	+B2b	750	+B2b	>5000
015 Chemical B101	-	-d	-	-d	200	+B2b	1050	-3b	200
016 Chemical B102	-	-b	-	-b	1590	+B2b	-	-2b	1600
017 Chemical B103	-	-	-	-	-	-2b	-	-2b	140
018 Chemical B104	-	-	-	-b	-	-3b	6460 or 548	+2B3b	3500

Group C

019 Chemical C01	16.3 or 49.6	+2Bb	11.0	+Bb	171 or 699	-2B	693 or 693	+2B	50
020 Chemical C02	16.3	+B2b	11.0	+Bb	200 or 699	-BB?	1640	+BB?	16
021 Chemical C03	16.3	+B2b	11.0	+Bb	200	+3B?	1640	+BB?d	16
022 Chemical C04	16.3	-B2bD	11.0	-B2bD	643	-B	6850 or 6850	+2B	6900
023 Chemical C05	16.3	+B	11.0	+B	200	+2B?	1290	+B2B?	16
024 Chemical C06	16.3	+B3b	11.0	+Bd	736	-Bbd	1640	+B2b	16
025 Chemical C07	-	-b	-	-b	-	-	-	-dw	140
026 Chemical C08	16.3	+B3bw	11.0	+Bd	736	-Bbdw	1640	+B2bw	16
027 Chemical C09	16.3	+B	11.0	+B	-	-d	1290	+B	16
028 Chemical C10	16.3	+B	11.0	+B	411	+BB?	1290	+BB?	210
029 Chemical C11	-	-	-	-b	603	+BB?	1290	+BB?	940
030 Chemical C12	-	-	-	-b	-	-	1290	+B	1300
031 Chemical C13	-	-	-	-b	-	-	1290	+B	1300
032 Chemical C14	-	-2X2w	-	-b	-	-2w	1290	+B2w	1300*
033 Chemical C15	16.3	+B2b	11.0	+B	-	-B?	1290	+B	16
034 Chemical C101	16.3	+B	11.0	+B	-	-	1290	+B	16
035 Chemical C102	-	-d	-	-d	397	+B	1180 or 450	+2B	450 (500 Expt.)
036 Chemical C103	16.3	+B	11.0	+B	-	-	1290	+B	16
037 Chemical C104	-	-d	-	-d	400	+B	1290 or 450	+2B	450
038 Chemical C105	16.3	+B	11.0	+B	-	-	1290	+B	16
039 Chemical C106	16.3	+Bb	11.0	+B	736	-B	1640	+B	16
040 Chemical C107	-	-b	-	-	736	-B	1640	+B	1600

Group D

041 Chemical D01	48 or 48	+2Bbd	149	-B?	244	+Bbd	-	-b	48
042 Chemical D02	-	-b	45.0	+B	-	-	-	-	45
043 Chemical D03	-	-b	45.0	+B	-	-	-	-b	45
044 Chemical D04	-	-b	45.0	+B	-	-	-	-	45
045 Chemical D05	40 or 40	+2Bbd	171	-B?b	247	+Bbd	-	-b	40
046 Chemical D101	-	-	-	-b	300 or 315	+2B	475	+BB?b	320
047 Chemical D102	-	-b	45.0	+B	-	-b	-	-b	45 (50 Expt.)

LEGEND TO TABLE 8

^a**MC No.:** The *MCASE* program automatically counts and enumerates each of the test compounds being analyzed.

^b**Compound Name:** The name of the test compound being analyzed in the *MCASE* QSAR tests.

^c**Maximum Tolerated Dose:** Additional information on the rat and mouse maximum tolerated dose (MTD) database modules **A77-A78, A81-A82, and A79-A80, A83-A84** is provided in **Section II.C.1**.

^d**Maximum tolerated dose activity / Maximum Tolerated Dose Modules:** The MTD activity (Act.) is expressed in mg/kg-bw/day. A default MTD value of '>1000.' is assigned under the human expert system for both rats and mice when the test compound has no *MCASE* structural alerts. The code 'NV' denotes a technical problem resulting in a 'no value' prediction. Additional information on the rat and mouse MTD database modules is provided in **Section II.C.1**.

^e**Structural Alerts / Maximum Tolerated Dose Modules:** An explanation for the different codes for molecular structural alerts identified by the *MCASE* program is provided in a glossary at the end of this report. Additional information on the *MCASE* structural alerts for the MTD database modules is provided in **Section II.C.1**.

^f**Overall Call:** The expert opinion call for the MTD is the median value of those of the four MTD modules which have one or more significant *MCASE* structural alerts, the lowest value if high variance is found among the modules (indicated by [†]), or a default value of 70 (rats) or 140 (mice) mg/kg-bw/day if no significant alerts were found for any module.

Table 9: Summary of the MC4PC Estimated and Actual Maximum Recommended Therapeutic Dose and No Effect Level Values of Forty-seven (47) Compounds in Adult Humans

MC No. ^a	Compound Name ^b	Maximum Recommended Therapeutic Doses and No Effect Levels (mg/kg-bw/day)					NOEL ^f
		MRTD Value ^e		Expert Opinions			
		A95 Act. ^d	Alerts ^a	A97 Act. ^d	Alerts ^a	Overall Call ^g MRTD	
TEST AND MODEL COMPOUNDS							
Group A							
001	Chemical A01	-	-	-	-	4.0	0.40
002	Chemical A02	-	-	-	-	4.0	0.40
003	Chemical A03	-	-B	70.0	+B	70	7.0
004	Chemical A04	6.50	-Bw	-	-bw	6.5	0.65
005	Chemical A05	-	-	-	-	4.0	0.40
006	Chemical A06	-	-w	-	-w	4.0	0.40
007	Chemical A07	-	-	-	-	4.0	0.40
008	Chemical A08	-	-w	-	-w	4.0	0.40
009	Chemical A09	-	-	-	-	4.0	0.40
010	Chemical A101	-	-	-	-	4.0	0.40
011	Chemical A102	-	-	-	-	4.0	0.40
012	Chemical A103	-	-w	4.87	+Bw	4.9	0.49
013	Chemical A104	-	-BD	70.0 or 5.00	+2Bb	38	3.8
Group B							
014	Chemical B01	-	-	6.67	+B?	6.7	0.67
015	Chemical B101	0.500	+Bbd	-	-	0.50	0.050
016	Chemical B102	-	-	-	-	4.0	0.40
017	Chemical B103	-	-	1.67	-B	1.7	0.17
018	Chemical B104	1.10	+B	-	-	1.1	0.11
Group C							
019	Chemical C01	0.800	+B	-	-	0.80	0.080
020	Chemical C02	0.0500	+Bb	13.3	+B?d	0.050	0.0050
021	Chemical C03	-	-b	10.0	+B?	10	1.0
022	Chemical C04	-	-b	5.00	-B	5.0	0.50
023	Chemical C05	-	-B?	16.8	+B?	17	1.7
024	Chemical C06	1.67 or 1.67	+2B	-	-B?d	1.7	0.17
025	Chemical C07	-	-	-	-b	4.0	0.40
026	Chemical C08	1.50 or 1.50	+2Bw	8.33	+B?dw	1.5	0.15
027	Chemical C09	0.0900	+BB?	-	-	0.090	0.0090
028	Chemical C10	0.400	+BB?	-	-	0.40	0.040
029	Chemical C11	0.400	+B	-	-	0.40	0.040
030	Chemical C12	-	-	-	-	4.0	0.40
031	Chemical C13	-	-	-	-b	4.0	0.40
032	Chemical C14	-	-w	-	-w	4.0	0.40
033	Chemical C15	-	-w	-	-w	4.0	0.40
034	Chemical C101	0.0500	-B?	-	-	0.050	0.0050
035	Chemical C102	0.625	-B?A	-	-I	0.63 (Expt. MRTD = 0.33)	0.063
036	Chemical C103	0.0500	+BB?A	-	-I	0.050 (Expt. MRTD = 0.10)	0.0050
037	Chemical C104	0.625	-B?	-	-	0.63	0.063
038	Chemical C105	0.0500	-B?w	-	-w	0.050	0.0050
039	Chemical C106	-	-	-	-	4.0	0.40
040	Chemical C107	-	-	-	-	4.0	0.40
Group D							
041	Chemical D01	-	-	5.00 or 5.41	+2B	5.2	0.52
042	Chemical D02	-	-B	6.67	+B?b	6.7	0.67
043	Chemical D03	0.400	-B	-	-B?	0.40	0.040
044	Chemical D04	-	-B	7.50	+B?b	7.5	0.75
045	Chemical D05	-	-d	-	-B	4.0	0.40
046	Chemical D101	-	-	-	-	4.0	0.40
047	Chemical D102	0.00300 or 0.333	+2BA	-	-dI	0.0030 [†] (Expt. MRTD = 0.010)	0.00030 [†]

LEGEND TO TABLE 9

^a**MC No.:** The *MC4PC* program automatically counts and enumerates each of the test compounds being analyzed.

^b**Compound Name:** The name of the test compound being analyzed in the *MC4PC* tests.

^c**Maximum Recommended Therapeutic Dose (MRTD) Value:** Additional information on the maximum recommended therapeutic dose (MRTD) database modules **A95** and **A97** is provided in **Section II.C.2**.

^d**Maximum Recommended Therapeutic Dose / Maximum Tolerated Dose Modules:** The MRTD activity (Act.) is expressed in mg/kg-bw/day. Additional information on the MRTD database modules is provided in **Section II.C.2**.

^e**Structural Alerts / Maximum Tolerated Dose Modules:** An explanation for the different codes for molecular structural alerts identified by the *MC4PC* program is provided in a glossary at the end of this report. Additional information on the *MC4PC* structural alerts for the MRTD dose database modules is provided in **Section II.C.2**.

^f**NOEL:** Additional information on the no effect level (NOEL) database modules **A95** and **A97** is provided in **Section II.C.2**.

^g**Overall Call:** The expert opinion call for the MRTD is the average value of the MRTD modules which have one or more significant *MC4PC* structural alerts, the lower value if high variance is found between the modules (indicated by †), or a default value of 4.0 mg/kg-bw/day for MRTD and 0.4 mg/kg-bw/day for NOEL if no significant alerts were found for either module.

Table 10: Summary of the MCASE Estimated and Actual Experimental Acute Toxicity Values of Forty-seven (47) Compounds in Rats and Mice

MC No. ^a	Rats or Mice Compound Name ^b	Acute Toxicity in (mg/kg) ^c		Expert Opinions		
		AL1 AL3 Act. ^d	Alerts ^e	AL2 AL4 Act. ^d	Overall Call ^f	
Acute Toxicity in Rats						
TEST AND MODEL COMPOUNDS						
Group A						
001	Chemical A01	-	-3w	5750	+B3w	>5000*
002	Chemical A02	-	-3w	5010	+BB?2b3w	5000*
003	Chemical A03	-	-2w	6610 or 5620	+2Bb2w	>5000*
004	Chemical A04	-	-2w	2880 or 6760	+2Bb2w	4800*
005	Chemical A05	-	-3w	4370 or 4790	+2B3w	4600*
006	Chemical A06	-	-6w	3240 or 3980	+2B6w	3600*
007	Chemical A07	229	+B6w	3470 or 4170	+2B6w	3500*
008	Chemical A08	-	-5w	4570	+B5w	4600*
009	Chemical A09	229	+B6w	3550 or 4270	+2B6w	3500*
010	Chemical A101	-	-3w	5370	+B3w	>5000*
011	Chemical A102	-	-3w	5010	+BB?2b3w	5000*
012	Chemical A103	-	-b3w	891 or 5620	+2B3w	3300*
013	Chemical A104	-	-3w	3630 or 4680 or 79.4	+3B3w	3600*
Group B						
014	Chemical B01	20900	+B	1120 or 617	+2B	1100
015	Chemical B101	316	+B	1120 or 1410	+2B	1100
016	Chemical B102	25700	+B	3800 or 1100	+2Bb	3800
017	Chemical B103	-	-	3630	+B	3600
018	Chemical B104	-	-	3240	+B2b	3200
Group C						
019	Chemical C01	-	-	4680	+B	4700
020	Chemical C02	-	-	2570 or 4680 or 24500	+3B	4700
021	Chemical C03	-	-	2040 or 4680	+2B	3400
022	Chemical C04	-	-	7940 or 4680 or 6030	+3B	6000
023	Chemical C05	-	-	2570 or 6760 or 4680	+3B	4700
024	Chemical C06	-	-b	3310	+B	3300
025	Chemical C07	-	-b	3720	+B?2b	3700
026	Chemical C08	-	-2w	3310	+B2w	3300*
027	Chemical C09	-	-b	20420	+B	>5000
028	Chemical C10	-	-	2630 or 4680	+2B	3700
029	Chemical C11	214	+B	2000	+B	1100
030	Chemical C12	214	+B	4570	+B2b	2400
031	Chemical C13	214	+B	6760 or 4570	+B2b	4600
032	Chemical C14	214	+Bw	4570	+B2bw	2400
033	Chemical C15	-	-	3800 or 4200	+B	4000
034	Chemical C101	-	-	4680 or 4570	+2Bb	4600
035	Chemical C102	-	-	-	-	3000
036	Chemical C103	-	-	20400 or 4680	+2B	>5000
037	Chemical C104	-	-	4570	+Bb	4600
038	Chemical C105	-	-	11000 or 4680 or 4570	+3Bb	4700
039	Chemical C106	-	-	4680	+BB?2b	4700
040	Chemical C107	-	-	3720	+B?2b	3700
Group D						
041	Chemical D01	3470 or 6170 or 234 or 1410	+4Bb2w	4680	+Bb2w	3500*
042	Chemical D02	-	-6w	5890 or 5370	+2Bb6w	5600*
043	Chemical D03	1780	+B6w	5250	+B6w	3500*
044	Chemical D04	-	-6w	3890 or 4470	+2B6w	4200*
045	Chemical D05	468 or 234 or 1380	+3Bb2w	4470	+Bb2w	920*
046	Chemical D101	-	-w	4370 or 5750	+2BB?2bw	5100
047	Chemical D102	-	-5w	562	+Bb5w	560*

**Acute Toxicity in Mice
TEST AND MODEL COMPOUNDS**

Group A

001 Chemical A01	7.41	+B?2w	-	-2w	7.4*
002 Chemical A02	20.9	+B?2w	-	-b2w	21*
003 Chemical A03	155 or 3890	+2BB?5w	3470 or 6760	+2B5w	3700*
004 Chemical A04	26.9	+B?5w	3470 or 6610	+2B5w	5000*
005 Chemical A05	38.9	+B?2w	3470	+B2w	3500*
006 Chemical A06	1070	+BB?7w	3470	+B7w	2300*
007 Chemical A07	1050	+BB?8w	3470	+B8w	2300*
008 Chemical A08	1150	+BB?b7w	-	-7w	1200*
009 Chemical A09	1120	+BB?b7w	3470	+B7w	2300*
010 Chemical A101	724	+BB?2w	-	-2w	720*
011 Chemical A102	20.9	+B?2w	-	-b2w	21*
012 Chemical A103	724	+BB?4w	3470	+B4w	2100*
013 Chemical A104	-	-4w	6460 or 14100	+2B4w	>5000*

Group B

014 Chemical B01	372	+B?	6610	+Bb	>5000
015 Chemical B101	-	-	-	-b	1500
016 Chemical B102	269	+BB?	15100 or 6310	+2Bbw	>5000
017 Chemical B103	-	-	6030	+B	>5000
018 Chemical B104	-	-	6610 or 6610	+Bb	>5000

Group C

019 Chemical C01	-	-xw	6760	+B2bw	>5000
020 Chemical C02	-	-	1320 or 6460	+2Bb	3900
021 Chemical C03	-	-	1320 or 6170	+2Bb	3700
022 Chemical C04	-	-	6760 or 3980	+2Bb	>5000
023 Chemical C05	-	-	1320 or 6610 or 158	+3Bb	1300
024 Chemical C06	-	-	6460	+BB?	>5000
025 Chemical C07	-	-2w	-	-2w	1500*
026 Chemical C08	-	-2w	6460	+B?2b2w	>5000*
027 Chemical C09	-	-w	6460	+BB?w	>5000
028 Chemical C10	-	-	6610 or 158	+2Bb	>5000
029 Chemical C11	145	+B	6460 or 162	+2B	160
030 Chemical C12	182	-BDw	6460 or 12300	+2Bw	>5000
031 Chemical C13	145	+Bw	3470 or 12600	+2Bw	3500
032 Chemical C14	166	+B2w	10200	+B2w	>5000*
033 Chemical C15	-	-w	6100 or 4120	+Bb	>5000
034 Chemical C101	-	-w	6760 or 12000	+2Bbw	>5000
035 Chemical C102	-	-w	6460	+Bw	>5000
036 Chemical C103	-	-w	6310	+Bbw	>5000
037 Chemical C104	-	-w	6310 or 10500	+2Bw	>5000
038 Chemical C105	-	-w	39.8 or 6460	+2Bbw	3200
039 Chemical C106	-	-	6610	+Bb	>5000
040 Chemical C107	-	-	6310	+B	>5000

Group D

041 Chemical D01	141	+B3w	6310	+B3w	3200*
042 Chemical D02	-	-b6w	3470	+B6w	3500*
043 Chemical D03	1350	+Bb6w	-	-6w	1400*
044 Chemical D04	-	-b6w	3470	+B6w	3500*
045 Chemical D05	141	+B3w	6310	+B3w	3200*
046 Chemical D101	-	-2w	-	-b2w	1500*
047 Chemical D102	977	+B5w	5890	+B5w	3400*

LEGEND TO TABLE 10

^a**MC No.:** The *MCASE* program automatically counts and enumerates each of the test compounds being analyzed.

^b**Compound Name:** The name of the test compound being analyzed in the *MCASE* QSAR tests.

^c**Acute Toxicity Dose:** Additional information on the rat and mouse acute toxicity dose database modules is provided in **Section II.C.3**.

^d**Acute Toxicity Dose Activity / Acute Toxicity Modules:** The acute toxicity is expressed in mg/kg-bw. Additional information on the rat and mouse acute toxicity database modules is provided in **Section II.C.3**.

Structural Alerts / Maximum Tolerated Dose Modules: An explanation for the different codes for molecular structural alerts identified by the *MCASE* program is provided in a glossary at the end of this report. The code 'NV' denotes a technical problem resulting in a 'no value' prediction. Additional information on the *MCASE* structural alerts for the acute toxicity database modules is provided in **Section II.C.3**.

Overall Call: The expert opinion call for the acute toxicity value is the median value of the acute toxicity values derived from significant *MC4PC* structural alerts, the lower value if high variance is found among the values, a value of '>5000' for exceptionally high doses, or a default value of 3000 (rats) or 1500 (mice) mg/kg-bw if no significant alerts were found for both modules.

Addendum Table 1: Summary of MC4PC Experimental Data Supporting Positive Carcinogenicity Predictions in Rats and Mice^a

MC No. ^b Compound Name ^c	Structural Alerts / Carcinogenicity Module ^d						Expert Opinions									
	AD2 Ra	AD3 MR	AD4 FR	AD5 Mi	AD6 MM	AD7 FM	No. SSA ^e	Overall Call ^f								
Test/Model Compound Activity from Table 1a^g																
002 Chemical A02	+Bb	+BB?bd	+2Bd	-	-	-	3	+								
Structural Alert ^h	Total Activity ⁱ						Structural Alert Activity ^k									
Mod. Frag. Cluster	Total	Total	Structural Alert Fragment ^l				Single Module									
No. No. No.	CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
AD2 {x21} {y21}	2032	43	{fragment #01}										15	2	1	12
AD3 {x31} {y31}	2032	43	{fragment #01}										15	3	0	12
AD4 {x41} {y41}	2032	43	{fragment #01}										13	2	1	10
Test/Model Compound Activity from Table 1a^g																
010 Chemical A101	+Bb	-Bbd	+Bd	-	-	-	3	+								
Structural Alert ^h	Total Activity ⁱ						Structural Alert Activity ^k									
Mod. Frag. Cluster	Total	Total	Structural Alert Fragment ^l				Single Module									
No. No. No.	CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
AD2 {x21} {y21}	2032	43	{fragment #01}										15	2	1	12
AD3 {x31} {y31}	2032	43	{fragment #01}										15	3	0	12
AD4 {x41} {y41}	2032	43	{fragment #01}										13	2	1	10
Test/Model Compound Activity from Table 1a^g																
011 Chemical A102	+Bb	+BB?bd	+2Bd	-	-	-	3	+								
Structural Alert ^h	Total Activity ⁱ						Structural Alert Activity ^k									
Mod. Frag. Cluster	Total	Total	Structural Alert Fragment ^l				Single Module									
No. No. No.	CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
AD2 {x21} {y21}	2032	43	{fragment #01}										15	2	1	12
AD3 {x31} {y31}	2032	43	{fragment #01}										15	3	0	12
AD4 {x41} {y41}	2032	43	{fragment #01}										13	2	1	10
Test/Model Compound Activity from Table 1a^g																
012 Chemical A103	+Bbw	-Bbdw	+Bbdw	-w	-w	-w	3	+								
Structural Alert ^h	Total Activity ⁱ						Structural Alert Activity ^k									
Mod. Frag. Cluster	Total	Total	Structural Alert Fragment ^l				Single Module									
No. No. No.	CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
AD2 {x21} {y21}	2032	43	{fragment #01}										15	2	1	12
AD3 {x31} {y31}	2032	43	{fragment #01}										15	3	0	12
AD4 {x41} {y41}	2032	43	{fragment #01}										13	2	1	10

MC No. ^b Compound Name ^c	Structural Alerts / Carcinogenicity Module ^d						Expert Opinions									
	AD2 Ra	AD3 MR	AD4 FR	AD5 Mi	AD6 MM	AD7 FM	No. SSA ^e	Overall Call ^f								
Test/Model Compound Activity from Table 1a ^g																
014 Chemical B01	+B	+B	+B	+B	-	+B	4	+								
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ⁱ		Structural Alert Fragment ^j				Structural Alert Activity ^k Single Module									
	CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
AD2 {x22} {y22}	800	13	{fragment #02}										3	0	0	3
AD3 {x32} {y32}	800	13	{fragment #02}										3	0	0	3
AD4 {x42} {y42}	800	13	{fragment #02}										3	0	0	3
AD7 {x72} {y72}	800	13	{fragment #02}										4	0	0	4

MC No. ^b Compound Name ^c	Structural Alerts / Carcinogenicity Module ^d						Expert Opinions									
	AD2 Ra	AD3 MR	AD4 FR	AD5 Mi	AD6 MM	AD7 FM	No. SSA ^e	Overall Call ^f								
Test/Model Compound Activity from Table 1a ^g																
016 Chemical B102	+B	+B	+B	+B	-	+B	4	+								
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ⁱ		Structural Alert Fragment ^j				Structural Alert Activity ^k Single Module									
	CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
AD2 {x22} {y22}	800	13	{fragment #02}										3	0	0	3
AD3 {x32} {y32}	800	13	{fragment #02}										3	0	0	3
AD4 {x42} {y42}	800	13	{fragment #02}										3	0	0	3
AD7 {x72} {y72}	800	13	{fragment #02}										4	0	0	4

MC No. ^b Compound Name ^c	Structural Alerts / Carcinogenicity Module ^d						Expert Opinions									
	AD2 Ra	AD3 MR	AD4 FR	AD5 Mi	AD6 MM	AD7 FM	No. SSA ^e	Overall Call ^f								
Test/Model Compound Activity from Table 1a ^g																
023 Chemical C05	-	+B?	-	-	+Bd	+BB?	3	+								
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ⁱ		Structural Alert Fragment ^j				Structural Alert Activity ^k Single Module									
	CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
AD3 {x33} {y33}	106	2	{fragment #03}										2	0	0	2
AD6 {x63} {y63}	408	8	{fragment #03}										4	0	0	4
AD7 {x73} {y73}	408	8	{fragment #03}										4	0	0	4

MC No. ^b Compound Name ^c	Structural Alerts / Carcinogenicity Module ^d						Expert Opinions									
	AD2 Ra	AD3 MR	AD4 FR	AD5 Mi	AD6 MM	AD7 FM	No. SSA ^e	Overall Call ^f								
Test/Model Compound Activity from Table 1a ^g																
028 Chemical C10	-	+B?	-	-	+B	+BB?	3	+								
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ⁱ		Structural Alert Fragment ^j				Structural Alert Activity ^k Single Module									
	CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
AD3 {x33} {y33}	106	2	{fragment #03}										2	0	0	2
AD6 {x63} {y63}	408	8	{fragment #03}										4	0	0	4
AD7 {x73} {y73}	408	8	{fragment #03}										4	0	0	4

MC No. ^b Compound Name ^c	Structural Alerts / Carcinogenicity Module ^d						Expert Opinions									
	AD2 Ra	AD3 MR	AD4 FR	AD5 Mi	AD6 MM	AD7 FM	No. SSA ^e	Overall Call ^f								
Test/Model Compound Activity from Table 1a ^g																
029 Chemical C11	-B	+BB?	-	-d	+B	+BB?	3	+								
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ⁱ		Structural Alert Fragment ^j				Structural Alert Activity ^k Single Module									
	CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
AD3 {x33} {y33}	106	2	{fragment #03}				2	0	0	2						
AD6 {x63} {y63}	408	8	{fragment #03}				4	0	0	4						
AD7 {x73} {y73}	408	8	{fragment #03}				4	0	0	4						

MC No. ^b Compound Name ^c	Structural Alerts / Carcinogenicity Module ^d						Expert Opinions									
	AD2 Ra	AD3 MR	AD4 FR	AD5 Mi	AD6 MM	AD7 FM	No. SSA ^e	Overall Call ^f								
Test/Model Compound Activity from Table 1a ^g																
047 Chemical D102	+BA	+BA	+BA	-BA	-BA	-BA	6	+A								
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ⁱ		Structural Alert Fragment ^j				Structural Alert Activity ^k Single Module									
	CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
AD2 {x21} {y21}	2032	43	{fragment #01}				15	2	1	12						
AD3 {x31} {y31}	2032	43	{fragment #01}				15	3	0	12						
AD4 {x41} {y41}	2032	43	{fragment #01}				13	2	1	10						
AD5 {x5m} {y5m}	169	3	{fragment #22}				1	0	0	1						
AD6 {x6m} {y6m}	169	3	{fragment #22}				1	0	0	1						
AD7 {x7m} {y7m}	169	3	{fragment #22}				1	0	0	1						

LEGEND TO ADDENDUM TABLE 1

^a**Positive Predictions:** This table presents critical data from the MC4PC program which support positive '+' predictions that are based upon the presence of ≥2 structurally similar alerts (SSA) that were reported in Table 1. The data identify the compounds in the training data set which share an alert identified in the test compounds, and they report the weighted toxicological response value of these compounds in CASE units.

^b**MC No.:** The MC4PC program automatically counts and enumerates each of the test compounds being analyzed.

^c**Compound Name:** The name of the test compound being analyzed in the MC4PC QSAR tests.

^d**Structural Alerts / Carcinogenicity Module:** An explanation for the different codes for molecular structural alerts identified by the MC4PC program is provided in a glossary at the end of this report. Additional information on the rodent carcinogenicity database modules AD2-7 is provided in Section II.A.1.

^e**No. SSA:** The total number of structurally similar alerts (SSA) identified by MC4PC in the test compound is used to predict the carcinogenic potential of the test compound. The SSA value refers to the SSA identified using the two groups of modules: 1) AD2-AD4 (rats); and 2) AD5-AD7 (mice).

^f**Overall Call:** The expert opinion call refers to the evaluation of the activity of the test compound, including: '+', active compounds have ≥2 SSA; '-', inactive compounds have <2 SSA; and '?' for compounds that are possibly active. See the glossary at the end of this report for other codes.

^g**Test/Model Compound Activity from Table 1:** Repeat of compound activities reported in Table 1.

^h**Structural alert:** The identity of the MC4PC structural alerts includes: (1) the code for the database module ('Mod. No. '), (2) the identification number of the structural alert assigned by MC4PC ('Frag. No. '), and (3) the identification number of the cluster of related alerts ('Cluster No. ').

ⁱ**Total Activity:** The total activity of the structural alert detected in all of the related database modules for this endpoint are described in terms of: (1) the total CASE unit activity of the alert ('Total CASE'), and (2) the total number of compounds in the training database modules which contained the alerts ('Total Chem.').

^j**Structural Alert Fragment:** The specific atoms and bonding contained in the structural alert.

^k**Structural Alert Activity:** The activity of the structural alert in individual modules is expressed in terms of the total number of compounds in the training data set containing the alert ('To'), and the number of these compounds which were inactive ('In.'), had marginal activities ('Ma.'), or were active ('Ac.').

Addendum Table 2: Summary of MC4PC Experimental Data Supporting Positive Teratogenicity Predictions in Mammals^a

MC No. ^b Compound Name ^c	Structural Alerts / Teratogen. Modules ^d					Expert Opinions	
	Rab. A50	Rats A51	Mice A52	Mam. A53	Rod. A54	No. SSA ^e	Overall Call ^f
Test/Model Compound Activity from Table 2^g							
020 Chemical C02	+B?	+BB?	-bd	+2B2B?	+B	3	+
Structural Alert ^h	Total Activity ⁱ					Structural Alert Activity ^k	
Mod. Frag. Cluster	Total	Total	Structural Alert Fragment ^l			Single Module	
No. No. No.	CASE	Chem.	1--2--3--4--5--6--7--8--9--10	To.	In.	Ma.	Ac.
A51 {x14} {y14}	260	6	{fragment #04}	2	0	0	2
A53 {x34} {y34}	260	6	{fragment #04}	2	0	0	2
A54 {x44} {y44}	260	6	{fragment #04}	2	0	0	2
Structural Alerts / Teratogen. Modules^d							
MC No. ^b Compound Name ^c	Rab. A50	Rats A51	Mice A52	Mam. A53	Rod. A54	No. SSA ^e	Overall Call ^f
Test/Model Compound Activity from Table 2^g							
025 Chemical C07	-	-d	+2B	+2B	-	2	+
Structural Alert ^h	Total Activity ⁱ					Structural Alert Activity ^k	
Mod. Frag. Cluster	Total	Total	Structural Alert Fragment ^l			Single Module	
No. No. No.	CASE	Chem.	1--2--3--4--5--6--7--8--9--10	To.	In.	Ma.	Ac.
A52 {x25} {y25}	407	10	{fragment #05}	4	0	0	4
A53 {x35} {y35}	407	10	{fragment #05}	6	0	0	6
Structural Alerts / Teratogen. Modules^d							
MC No. ^b Compound Name ^c	Rab. A50	Rats A51	Mice A52	Mam. A53	Rod. A54	No. SSA ^e	Overall Call ^f
Test/Model Compound Activity from Table 2^g							
032 Chemical C14	-xw	+B	-	+B	-B	3	+
Structural Alert ^h	Total Activity ⁱ					Structural Alert Activity ^k	
Mod. Frag. Cluster	Total	Total	Structural Alert Fragment ^l			Single Module	
No. No. No.	CASE	Chem.	1--2--3--4--5--6--7--8--9--10	To.	In.	Ma.	Ac.
A51 {x17} {y17}	323	7	{fragment #07}	2	0	0	2
A53 {x37} {y37}	323	7	{fragment #07}	3	0	0	3
A54 {x47} {y47}	323	7	{fragment #07}	2	0	0	2
Structural Alerts / Teratogen. Modules^d							
MC No. ^b Compound Name ^c	Rab. A50	Rats A51	Mice A52	Mam. A53	Rod. A54	No. SSA ^e	Overall Call ^f
Test/Model Compound Activity from Table 2^g							
035 Chemical C102	+BA	-dM	+BA	+BA	+BA	4	+A
Structural Alert ^h	Total Activity ⁱ					Structural Alert Activity ^k	
Mod. Frag. Cluster	Total	Total	Structural Alert Fragment ^l			Single Module	
No. No. No.	CASE	Chem.	1--2--3--4--5--6--7--8--9--10	To.	In.	Ma.	Ac.
A52 {x25} {y25}	407	10	{fragment #05}	4	0	0	4
A53 {x35} {y35}	407	10	{fragment #05}	6	0	0	6
A50 {x0n} {y0n}	178	4	{fragment #23}	2	0	0	2
A54 {x4n} {y4n}	178	4	{fragment #23}	2	0	1	1

MC No. ^b Compound Name ^c	Structural Alerts / Teratogen. Modules ^d					Expert Opinions										
	Rab. A50	Rats A51	Mice A52	Mam. A53	Rod. A54	No. SSA ^e	Overall Call ^f									
Test/Model Compound Activity from Table 2 ^g																
037 Chemical C104	+B	-d	-	-	+B	2	+									
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ^j		Structural Alert Fragment ⁱ			Structural Alert Activity ^k										
	Total CASE	Total Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
A50 {x0n} {y0n}	178	4	{fragment #23}										2	0	0	2
A54 {x4n} {y4n}	178	4	{fragment #23}										2	0	1	1

MC No. ^b Compound Name ^c	Structural Alerts / Teratogen. Modules ^d					Expert Opinions										
	Rab. A50	Rats A51	Mice A52	Mam. A53	Rod. A54	No. SSA ^e	Overall Call ^f									
Test/Model Compound Activity from Table 2 ^g																
039 Chemical C106	-d	-2d	+2B	+2B	-d	2	+									
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ^j		Structural Alert Fragment ⁱ			Structural Alert Activity ^k										
	Total CASE	Total Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
A52 {x25} {y25}	407	10	{fragment #05}										4	0	0	4
A53 {x33} {y33}	407	10	{fragment #05}										6	0	0	6

MC No. ^b Compound Name ^c	Structural Alerts / Teratogen. Modules ^d					Expert Opinions										
	Rab. A50	Rats A51	Mice A52	Mam. A53	Rod. A54	No. SSA ^e	Overall Call ^f									
Test/Model Compound Activity from Table 2 ^g																
040 Chemical C107	-	-2d	+2B	+2B	-	2	+									
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ^j		Structural Alert Fragment ⁱ			Structural Alert Activity ^k										
	Total CASE	Total Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
A52 {x25} {y25}	407	10	{fragment #05}										4	0	0	4
A53 {x35} {y35}	407	10	{fragment #05}										6	0	0	6

MC No. ^b Compound Name ^c	Structural Alerts / Teratogen. Modules ^d					Expert Opinions										
	Rab. A50	Rats A51	Mice A52	Mam. A53	Rod. A54	No. SSA ^e	Overall Call ^f									
Test/Model Compound Activity from Table 2 ^g																
046 Chemical D101	-	-bA	-	+BA	+BA	2	+A									
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ^j		Structural Alert Fragment ⁱ			Structural Alert Activity ^k										
	Total CASE	Total Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
A53 {x38} {y38}	171	6	{fragment #08}										3	1	0	2
A54 {x48} {y48}	171	6	{fragment #08}										3	1	0	2

LEGEND TO ADDENDUM TABLE 2

^a**Positive Predictions:** This table presents critical data from the MC4PC program which support positive '+' predictions that are based upon the presence of ≥2 structurally similar alerts (SSA) that were reported in Table 2. The data identify the compounds in the training data set which share an alert identified in the test compounds, and they report the weighted toxicological response value of these compounds in CASE units.

^b**MC No.:** The MC4PC program automatically counts and enumerates each of the test compounds being analyzed.

^c**Compound Name:** The name of the test compound being analyzed in the MC4PC QSAR tests.

^d**Structural Alerts / Teratogenicity Module:** An explanation for the different codes for molecular structural alerts identified by the MC4PC program is provided in a glossary at the end of this report. Additional information on the individual mammalian teratogenicity database modules A50-4 is provided in Section II.A.2.

^e**No. SSA:** The total number of structurally similar alerts (SSA) identified by MC4PC in the test compound is used to predict the teratogenic potential of the test compound. The SSA value refers to the SSA identified using the A50-4 modules.

^f**Overall Call:** The expert opinion call refers to the evaluation of the activity of the test compound, including: '+', active compounds have ≥2 SSA; '-', inactive compounds have <2

SSA; and '?' for compounds that are possibly active. See the glossary at the end of this report for other codes.

°Test/Model Compound Activity from Table 2: Repeat of compound activities reported in **Table 2**.

°Structural alert: The identity of the *MC4PC* structural alerts includes: (1) the code for the database module ('Mod. No. '), (2) the identification number of the structural alert assigned by *MC4PC* ('Frag. No. '), and (3) the identification number of the cluster of related alerts ('Cluster No. ').

°Total Activity: The total activity of the structural alert detected in all of the related database modules for this endpoint are described in terms of: (1) the total CASE unit activity of the alert ('Total CASE'), and (2) the total number of compounds in the training database modules which contained the alerts ('Total Chem.').

°Structural Alert Fragment: The specific atoms and bonding contained in the structural alert.

°Structural Alert Activity: The activity of the structural alert in individual modules is expressed in terms of the total number of compounds in the training data set containing the alert ('To'), and the number of these compounds which were inactive ('In.'), had marginal activities ('Ma.'), or were active ('Ac.').

Addendum Table 3: Summary of MC4PC Experimental Data Supporting Positive Mutagenicity Predictions in *Salmonella typhimurium*^a

MC No. ^b Compound Name ^c	Structural Alerts / <i>Salmonella t.</i> Module ^d													Expert Opinions	
	A2J	A6K	A6L	A6M	A6O	A6P	A6R	A6S	A6U	A6V	A6W	A6X	A6Z	No. SSA ^e	Overall Call ^f
Test/Model Compound Activity from Table 3 ^g															
041 Chemical D01	+2B	-B3D	-	+2B	+B	+BB?2w	-2w	-b2w	+2B2w	-BDd	-	-B	-B3D	12	+
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ⁱ		Structural Alert Fragment ^j							Structural Alert Activity ^k					
	Total	Total	Structural Alert Fragment ^j							Single Module					
CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
A2J {xJ9} {yJ9}	42616	1332	{fragment #09}							311	48	0	263		
A6K {xK9} {yK9}	42616	1332	{fragment #09}							264	122	9	133		
A6O {xO9} {yO9}	42616	1332	{fragment #09}							265	96	12	157		
A6P {xP9} {yP9}	42616	1332	{fragment #09}							132	45	7	80		
A6U {xU9} {yU9}	42616	1332	{fragment #09}							139	53	4	82		
A6Z {xZ9} {yZ9}	42616	1332	{fragment #09}							221	87	8	126		
A6M {xM9} {yM9}	1062	36	{fragment #09}							18	6	1	11		
A6X {xX9} {yX9}	1062	36	{fragment #09}							18	6	2	10		
A6V {xV9} {yV9}	700	20	{fragment #09}							20	5	2	13		
A6M {xMa} {yMa}	180	4	{fragment #10}							4	0	0	4		
A6P {xPa} {yPa}	1960	70	{fragment #10}							70	27	4	39		
A6U {xUa} {yUa}	3774	111	{fragment #10}							111	47	1	63		

MC No. ^b Compound Name ^c	Structural Alerts / <i>Salmonella t.</i> Module ^d													Expert Opinions	
	A2J	A6K	A6L	A6M	A6O	A6P	A6R	A6S	A6U	A6V	A6W	A6X	A6Z	No. SSA ^e	Overall Call ^f
Test/Model Compound Activity from Table 3 ^g															
043 Chemical D03	+B	+B	-B	-	-	-B4w	-B4w	-6w	-4w	+B	+B	-	-	7	+
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ⁱ		Structural Alert Fragment ^j							Structural Alert Activity ^k					
	Total	Total	Structural Alert Fragment ^j							Single Module					
CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
A2J {xJb} {yJb}	4816	151	{fragment #11}							65	13	0	52		
A6P {xPb} {yPb}	4816	151	{fragment #11}							45	16	6	23		
A6R {xRb} {yRb}	4816	151	{fragment #11}							41	18	0	23		
A6K {xKb} {yKb}	311	4	{fragment #11}							1	0	0	1		
A6L {xLb} {yLb}	311	4	{fragment #11}							1	0	0	1		
A6V {xVb} {yVb}	311	4	{fragment #11}							1	0	0	1		
A6W {xWb} {yWb}	311	4	{fragment #11}							1	0	0	1		

MC No. ^b Compound Name ^c	Structural Alerts / <i>Salmonella t.</i> Module ^d													Expert Opinions	
	A2J	A6K	A6L	A6M	A6O	A6P	A6R	A6S	A6U	A6V	A6W	A6X	A6Z	No. SSA ^e	Overall Call ^f
Test/Model Compound Activity from Table 3 ^g															
045 Chemical D05	+B	-B3D	-	+B	+B	+B2w	-2w	-2w	-BD2w	+Bd	-	-B	-B3D	9	+
Structural Alert ^h Mod. Frag. Cluster No. No. No.	Total Activity ⁱ		Structural Alert Fragment ^j							Structural Alert Activity ^k					
	Total	Total	Structural Alert Fragment ^j							Single Module					
CASE	Chem.	1	2	3	4	5	6	7	8	9	10	To.	In.	Ma.	Ac.
A2J {xJ9} {yJ9}	42616	1332	{fragment #09}							311	48	0	263		
A6K {xK9} {yK9}	42616	1332	{fragment #09}							264	122	9	133		
A6O {xO9} {yO9}	42616	1332	{fragment #09}							265	96	12	157		
A6P {xP9} {yP9}	42616	1332	{fragment #09}							132	45	7	80		
A6U {xU9} {yU9}	42616	1332	{fragment #09}							139	53	4	82		
A6Z {xZ9} {yZ9}	42616	1332	{fragment #09}							221	87	8	126		
A6M {xM9} {yM9}	1062	36	{fragment #09}							18	6	1	11		
A6X {xX9} {yX9}	1062	36	{fragment #09}							18	6	2	10		

LEGEND TO ADDENDUM TABLE 3

^aPositive Predictions: This table presents critical data from the *MC4PC* program which support positive '+' predictions that are based upon the presence of ≥ 2 structurally similar alerts (**SSA**) that were reported in **Table 3**. The data identify the compounds in the training data set which share an alert identified in the test compounds, and they report the weighted toxicological response value of these compounds in CASE units.

^bMC No.: The *MC4PC* program automatically counts and enumerates each of the test compounds being analyzed.

^cCompound Name: The name of the test compound being analyzed in the *MC4PC* QSAR tests.

^dStructural Alerts / *Salmonella typhimurium* Mutagenicity Modules: An explanation for the different codes for molecular structural alerts identified by the *MC4PC* program is provided in a glossary at the end of this report. Additional information on the individual *Salmonella typhimurium* mutagenicity database modules (**A2J, A6K-A6M, A6O, A6P, A6R, A6S, A6U-A6X, and A6Z**) is provided in **Section II.A.3**.

^eNo. SSA: The total number of structurally similar alerts (**SSA**) identified by *MC4PC* in the test compound is used to predict the mutagenic potential of the test compound. The SSA value refers to the SSA identified using the **A2J, A6K-A6M, A6O, A6P, A6R, A6S, A6U-A6X, and A6Z** modules.

^fOverall Call: The expert opinion call refers to the evaluation of the activity of the test compound, including: '+', active compounds have ≥ 2 SSA; '-', inactive compounds have < 2 SSA; and '+?' for compounds that are possibly active. See the glossary at the end of this report for other codes.

^gTest/Model Compound Activity from Table 3: Repeat of compound activities reported in **Table 3**.

^hStructural alert: The identity of the *MC4PC* structural alerts includes: (1) the code for the database module ('Mod. No.'), (2) the identification number of the structural alert assigned by *MC4PC* ('Frag. No.'), and (3) the identification number of the cluster of related alerts ('Cluster No.').

ⁱTotal Activity: The total activity of the structural alert detected in all of the related database modules for this endpoint are described in terms of: (1) the total CASE unit activity of the alert ('Total CASE'), and (2) the total number of compounds in the training database modules which contained the alerts ('Total Chem.').

^jStructural Alert Fragment: The specific atoms and bonding contained in the structural alert.

^kStructural Alert Activity: The activity of the structural alert in individual modules is expressed in terms of the total number of compounds in the training data set containing the alert ('To'), and the number of these compounds which were inactive ('In.'), had marginal activities ('Ma.'), or were active ('Ac.').

Figure 1a: Chemical structures of nine (9) test compounds in Group A

{structure of Chemical A01}

{structure of Chemical A02}

Chemical A01

Chemical A02

{structure of Chemical A03}

{structure of Chemical A04}

Chemical A03

Chemical A04

{structure of Chemical A05}

{structure of Chemical A06}

Chemical A05

Chemical A06

{structure of Chemical A07}

{structure of Chemical A08}

Chemical A07

Chemical A08

{structure of Chemical A09}

Chemical A09

Figure 1b: Chemical structures of one test compound in Group B

{structure of Chemical B01}

Chemical B01

Figure 1c: Chemical structures of fifteen (15) test compounds in Group C

{structure of Chemical C01}

Chemical C01

{structure of Chemical C02}

Chemical C02

{structure of Chemical C03}

Chemical C03

{structure of Chemical C04}

Chemical C04

{structure of Chemical C05}

Chemical C05

{structure of Chemical C06}

Chemical C06

{structure of Chemical C07}

{structure of Chemical C08}

Chemical C07

Chemical C08

{structure of Chemical C09}

{structure of Chemical C10}

Chemical C09

Chemical C10

{structure of Chemical C11}

{structure of Chemical C12}

Chemical C11

Chemical C12

{structure of Chemical C13}

{structure of Chemical C14}

Chemical C13

Chemical C14

{structure of Chemical C15}

Chemical C15

Figure 1d: Chemical structure of five (5) test compounds in Group D

{structure of Chemical D01}

Chemical D01

{structure of Chemical D02}

Chemical D02

{structure of Chemical D03}

Chemical D03

{structure of Chemical D04}

Chemical D04

{structure of Chemical D05}

Chemical D05

Figure 2a: Chemical structures of four (4) model compounds in Group A

{structure of Chemical A101}

{structure of Chemical A102}

Chemical A101

Chemical A102

{structure of Chemical A103}

{structure of Chemical A104}

Chemical A103

Chemical A104

Figure 2b: Chemical structures of four (4) model compounds in Group B

{structure of Chemical B101}

{structure of Chemical B102}

Chemical B101

Chemical B102

{structure of Chemical B103}

{structure of Chemical B104}

Chemical B103

Chemical B104

Figure 2c: Chemical structures of seven (7) model compounds in Group C

{structure of Chemical C101}

Chemical C101

{structure of Chemical C102}

Chemical C102

{structure of Chemical C103}

Chemical C103

{structure of Chemical C104}

Chemical C104

{structure of Chemical C105}

Chemical C105

{structure of Chemical C106}

Chemical C106

{structure of Chemical C107}

Chemical C107

Figure 2d: Chemical structures of two (2) model compounds in Group D

{structure of Chemical D101}

{structure of Chemical D102}

Chemical D101

Chemical D102

Abbreviations & Definitions

/

Predicted Toxicological Activities

"+"	positive containing ≥ 2 significant structurally similar alerts
"+?"	possibly positive containing ≥ 2 significant, structurally similar or dissimilar alerts which were rejected based upon human expert system rules
"-"	negative
"m"	marginal response is assigned to equivocal/weak activities that are of questionable biological/statistical significance
"*"	poor coverage
"†"	high variance among predicted values predictions
"Expert Opinion"	the principle investigator's expert assessment of MC4PC program data and not the default prediction of the program
"NV"	predictions were flawed due to a program logic error and were evaluated as not valid
"SSA"	significant and structurally similar alerts

Human Expert System Rules for Evaluation of MC4PC Experimental Data

de	≥ 2 significant alerts which are rejected because the test compound alert is in a different molecular environment compared to the training compounds
deg	≥ 2 significant alerts which are rejected because MC4PC evaluates them as weakly significant and degenerate
bad alert	an alert that has a abnormally high ratio of inactive and/or marginals compounds to active compounds
qsar	an alert that is rejected because the total QSAR value is < 30 CASE units

Actual Experimental Toxicological (or Adverse Clinical) Activities ("Act.")

"A"	active response is reserved for experimental activities that are biologically/statistically significant at two or more related endpoints (<i>i.e.</i> , trans-gender/species carcinogenicity, trans-species teratogenicity, adverse immunological effect at ≥ 2 adverse immunological effect endpoints, <i>etc.</i>)
"A?"	possibly active response is designated for experimental activities that are biologically/statistically significant at a single endpoint (<i>e.g.</i> , gender-specific carcinogenicity in rodents, single-species teratogenicity in mammals, single adverse immunological effect in adults, <i>etc.</i>)
"M"	marginal response is assigned to equivocal/weak activities that are of questionable biological/statistical significance
"I"	inactive

MC4PC non-Hydrogen Atoms

"Br, C, Cl, F, I, N, O, P, S"	aliphatic atoms
"."	atom common to two rings
"c,n,s"	aromatic atoms
"^"	fragment part of small ring (3-4 atoms)
"<3-CH2>"	CH ₂ side chain on third atom
">,<"	atom with heteroatom substituted group
"\$"	triple bond
"#"	double bond out of fragment

MC4PC Structural Alerts (Biophores)

"B"	significant alert (≥ 150 total CASE units)
"B?"	possibly significant alert (100-150 total CASE units)
"b"	non-significant alert that is rejected (< 100 total CASE units)
"X"	significant unknown fragment alert (≥ 150 total CASE units)
"X?"	possibly significant unknown fragment alert (100-150 total CASE units)
"x"	non-significant unknown fragment alert that is rejected (< 100 total CASE units)
"w"	unknown molecular fragment identified in the test compound
"D"	deactivating fragment
"d"	non-significant deactivating fragment that is rejected (present in < 8 compounds)

Abbreviations for the Different Chemical Activities

"Salm."	mutagenicity in <i>Salmonella typhimurium</i>
"Carc."	carcinogenicity in rodents: rats and mice
"Terat."	teratogenicity in mammals: rabbits, rats and mice
"Liver"	adverse liver effect in adult humans
"Imm."	adverse immunological effect in adult humans
"Card."	adverse cardiological effect in adult humans
"MTD"	maximum tolerated dose in rodents: rats and mice
"NOEL"	no effect level dose in adult humans
"MRTD"	maximum recommended therapeutic dose in adult humans
"LD50"	acute toxicity in rodents
"\$\$\$"	proprietary test chemical and data
"S.I."	similarity index measure of structural similarity determined by <i>ISIS™/HOST</i> software
"Bio."	bioavailability determined by <i>MC4PC</i> software
"LR"	Lipinski's rule of five; compound is predicted bioavailable (LR+) or compound may not be bioavailable (LR+?)

Glossary of Acronyms and Abbreviations

ADME	adsorption, distribution, metabolism, excretion, and bioavailability
ADR	FDA/CDER adverse drug reaction database
AERS	FDA/CDER adverse event reporting system database
CAS	Chemical Abstract Service registry
CASE Unit	standard <i>MC4PC</i> program toxicological activity unit(s)
CASE_{TOT}	total CASE unit activity
CDER	Center for Drug Evaluation and Research; the Center
CFSAN	Center for Food Safety and Applied Nutrition
CRADA	cooperative research and development agreement
ES	human expert system
FDA	The U.S. Food and Drug Administration; the Agency
FCS	food contact substance
ICSAS	Informatics and Computational Safety Analysis Staff
IND	investigational new drug application
MC4PC	multiple computer automated structure evaluation program; also <i>MC</i> , <i>MCASE</i>
MTA	material transfer agreement
MW	molecular weight
NTP	National Toxicology Program
NDA	new drug application
QSAR	quantitative structure activity relationships
SA(s)	structural alert (biological activity correlated chemical molecular fragment)
SRS	FDA/CDER Spontaneous Reporting System