Occupational Knowledge International

Ms. Jennifer Butler
Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

4236 '00 MAR 14 P1:48

March 6, 2000

Re: Petition to Restrict Sale of Coal Tar-Containing Products

Dear Ms. Butler,

Over the past two years I have worked with the California Environmental Protection Agency (Cal-EPA) on preparing a risk assessment for coal tar-containing products as part of litigation brought under California's Proposition 65. Recently Cal-EPA has completed a review of the health effects of coal tar and has proposed a preliminary no significant risk level for litigation purposes. This review included recent toxicological studies, and research on absorption with human subjects, that have been reported since FDA last addressed the safety of coal tar shampoos.

Action Requested

We are petitioning FDA to initiate a formal review of the use, sale and distribution of coal tar shampoo, soap and ointments under the requirements of the Federal Food, Drug, and Cosmetic Act and the Fair Packaging and Labeling Act. We believe that in light of the evidence presented, FDA should request that the Department of Justice take appropriate action to restrict the sale and distribution of these products to prescription sales. Furthermore, current labeling requirements are insufficient and require additional warning language to protect public health.

Statement of Grounds

Coal tar is one of the first known human carcinogens. Animal studies linking coal tar to cancer were first conducted in the 1890s. Coal tar, and several of the constituent PAHs in coal tar, were among the first carcinogens to be listed under California's Proposition 65. According to IARC, coal tar is causally associated with cancer in humans. Studies with human volunteers have demonstrated that PAHs can be readily absorbed from the use of these shampoo products and epidemiological studies have demonstrated that coal tar can cause skin and other systematic cancers. This information lead the European Union to decide to ban these products in 1997.

In addition, we have located a very well conducted dermal carcinogenicity bioassay study from Europe that is not yet published. The research, conducted

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1255 Post Street, Suite 437 • San Francisco, CA 94109 • 415/441-5199 • Fax: 415/441-5767

at the Fraunhofer Institute of Toxicology, provides the best quantitative evidence of the carcinogenicity of coal tar in mice. This study was employed by Cal-EPA and by our consultant, Dr. Lee Shull of Newfields, to conduct a quantitative risk assessment. I have enclosed a copy of Dr. Shull's report dated October 29, 1999.

Usage patterns indicate that the use of coal tar shampoos is not limited to episodic dandruff outbreaks. Research has indicated that a significant percentage of purchasers use these products daily over many years.

Furthermore, the following should be considered by FDA:

• Coal tar is added to these products to treat a condition (dandruff) for which there is no evidence of its efficacy. As a result, these products cannot be sold in Canada as dandruff shampoos.

• Coal tar is the first known carcinogen identified from experimental toxicological research published in 1915. In the 1940s several researchers published articles indicating that coal tar causes skin cancer in humans. Evidence that coal tar can be absorbed from shampoo was first published in 1984.

• The use of coal tar in over the counter products is controversial in the medical community. Coal tar products were banned by Germany in 1995 and by the European Union in 1997 as a result of the potential health effects.

• Benzo[a]pyrene (BAP) is one of the most potent carcinogens known. This compound has received extensive attention as a carcinogen that is common in charcoal cooked meat and in cigarettes. However, the concentration of BAP in a single application of some coal tar shampoos is 470,000 times greater than in a cigarette and about 200 times greater than in a hamburger.

I have attached a copy of the Fraunhofer study, an addendum to the study indicating the constituents of the mixtures tested, the Newfields risk assessment report, and a partial list of supplemental references. I would be pleased to meet with FDA staff to provide additional information. Please contact me if you have any questions via email at okincpg@aol.com or at (415) 441-5199.

To the best of my knowledge, this petition includes all relevant information concerning this request.

Sincerely,

Perry Gottesfeld, M.P.H.
Executive Director

cc: Linda Katz, FDA, David Gaylor, NCTR

Occupational Knowledge International

Ms. Jennie Butler
Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

March 21, 2000

Re: Petition to Restrict Sale of Coal Tar-Containing Products

Dear Ms. Butler,

As we discussed, this letter is an attachment to our previously submitted petition. No environmental impact statement is required for this petition.

In addition, we understand that the Newfields document we included as an attachment will be publicly available. Please distribute the document as needed.

Please contact me if you have any questions via email at okincpg@aol.com or at (415) 441-5199.

To the best of my knowledge, this petition includes all relevant information concerning this request.

Sincerely,

Perry Gottesfeld

Perry Gottesfeld, M.P.H.
Executive Director

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Occupational Knowledge International
Coal Tar Toxicological Studies
Partial list of supplemental References:

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NEWFIELDS

ATTORNEY-CLIENT PRIVILEGE

October 29, 1999

Mr. Mark Pollock
Law Office Of Mark Pollock
1207 Coombs Street
Napa, California 94559

Dear Mr. Pollock:

A dermal cancer potency factor for coal tar shampoo of **0.7 (mg/day)$^{-1}$** was derived using the linearized multi-stage model GLOBAL 86 (Howe et al., 1986). The slope factor was used to calculate a Proposition 65 No Significant Risk Level (NSRL) of **2×10^{-5} mg/d** (0.02 μg/d). Consistent with the California Office Environmental Health Hazard Assessment's (OEHHA) memo from Page Parker to Susan Fiering the NSRL applies to the applied dose of coal tar in shampoo "that remains as a persistent residue following application."

Introduction

The "No Significant Risk Level" (NSRL), under the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), represents a daily intake level calculated to result in a cancer risk not exceeding one excess case of cancer in 100,000 individuals exposed over a 70-year lifetime. A NSRL for coal tar use in shampoo was calculated by NEWFIELDS. To be representative of the use of shampoo, the NSRL was calculated based on evidence of carcinogenic effects from dermal application of coal tar.

Methods

Data

NEWFIELDS used data from the dermal carcinogenicity study by the Fraunhofer Institute of Toxicology (1997). The study measured the incidence of skin tumors in male CD-1 mice from the direct dermal application of coal tar at different concentrations in toluene. The study evaluated two different coal tar substances. One contained approximately 10 μg Benzo(a)Pyrene [B(a)P]/ g of coal tar. This coal tar was referred to as CPT-1. The other coal tar substance, CPT-2, contained approximately 275 μg B(a)P/ g of coal tar. The study lasted for 78 weeks with dermal applications of coal tar performed twice weekly. The CPT-1 treated mice did not show a statistically significant deviation in dermal tumor incidence from the control. The CPT-2 treated group showed statistical increases in tumor incidence with increasing coal tar doses. Therefore, the data from the CPT-2 treated group was used to calculate a cancer potency factor. The dose

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Table 1. Results from Dermal Carcinogenicity Study (Fraunhofer Institute of Toxicology, 1997)

Group	Coal Tar per Treatment (mg)	Treatments/ Week	Days/Week	Treatments/ Day	Coal Tar Dose (mg/d)	Total Animals	Animals with Tumors
CTP2	0	2	7	0.29	0.0	124	1
CTP2	0.1	2	7	0.29	0.03	62	1
CTP2	0.3	2	7	0.29	0.09	62	3
CTP2	1	2	7	0.29	0.3	62	9
CTP2	3	2	7	0.29	0.9	62	23
CTP2	9	2	7	0.29	2.6	61	20

levels of the CPT-2 treatment were 0.1, 0.3, 1, 3, and 9 mg coal tar per treatment. The CPT-2 high dose group exhibited ulceration of the skin and with complete focal loss of the epidermis. This high dose treatment set of the CTP-2 group was terminated early. The high dose group was not used in the potency evaluation. Table 1 lists the results of the dermal carcinogen study for the CPT-2 group.

Potency Factor

NEWFIELDS performed an evaluation of the dermal cancer data from the Fraunhofer study to estimate a human dermal cancer potency factor. The tumor incidence data was analyzed using the linearized multistage model (LMS) GLOBAL86 (Howe et al., 1986), and the 95% confidence interval of the slope of the dose response curve (q1*) was calculated. A typical assessment approach for calculating a human potency factor includes calculating an animal slope factor with the units of the inverse of mass of exposure per mass body weight per day $(mg/kg\text{-}d)^{-1}$, which is then scaled based on animal to human body weight ratio. The resultant human slope factor would be in the standard units of $(mg/kg\text{-}d)^{-1}$. This method utilizing the body weight parameter is necessary to account for systemic distribution of an absorbed dose that would then be available to act on a target organ. However, given that the effects are dermal due to local application exposure and is not dependent on absorption and distribution within the body, the use of body weight adjustments are not applicable for this evaluation. Therefore, NewFields applied a methodology similar to a draft EPA methodology developed for calculating risk from dermal exposure to B(a)P (EPA, 1997). The approach outlined by EPA for assessing risk from point of exposure cancer makes use of the fact that "the systemic distribution of absorbed doses is not relevant." Therefore, body weight is not a necessary factor. The EPA assumed that "the application of an equivalent dose to 1 cm^2 of skin from either a mouse or human would have the equal probability of inducing a tumor." The resultant slope factor calculated from animal data would not be scaled to humans by body weight and would have the units of inverse the mass of dermal dose per day $(mg/d)^{-1}$. This approach differs from the standard OEHHA method, which assumes that the risk assessment takes into account the systemic distribution of a dose by using body weight scaling. The draft EPA approach outlines the rationale why the body weight factor should not be applied to assessment of effects from local application. Therefore, an animal slope factor based on mass per day (mg/d) dosages was estimated and was not body weight scaled for human application.

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Results

The resultant q1* slope factor from GLOBAL86 was 0.7 $(mg/d)^{-1}$. The associated p-value, which when greater than 0.01 indicates that the model fit to the data is statistically adequate, was 0.95. The value was not scaled before being applied for human health assessment. The NSRL was calculated using the following equation:

$$\text{NSRL} = \frac{\text{Target Risk}}{\text{CSF}}$$

where;

Target Risk	=	1×10^{-5}, Proposition 65 default
CSF	=	Cancer Slope Factor, 0.7 $(mg/d)^{-1}$.

The resultant NSRL for coal tar is **2×10^{-5} mg/day** (0.02 μg/d).

Discussion

Based on the OEHHA memo from Page Parker to Susan Fiering, August, 1999, the NSRL would apply to the amount of coal tar in "shampoo that remains as a persistent residue following application." Using the NSRL, NewFields calculated a coal tar content in shampoo that would result in an exposure equivalent to the NSRL. This was done using the following equation that is used to calculate a Lifetime Average Daily Dose (LADD).

$$\text{LADD}\,(mg/day) = \frac{(C \times AR \times CF \times ED \times RF\ )}{AT}$$

where:

C	=	coal tar concentration in shampoo (mg/g)
AR	=	shampoo application or use rate (oz/year)
CF	=	conversion factor, 28.35 g/ oz of shampoo
ED	=	exposure duration (years)
RF	=	residue factor (*e.g.*, percent of dermal application that remains in contact on the skin persistently)
AT	=	averaging time; the time over which the exposure is averaged (days)

In solving for a coal tar concentration in shampoo, the LADD is set equal to the NSRL and the equation is rearranged and solved for the coal tar concentration (C):

$$C = \frac{(\text{LADD} \times AT)}{(\ AR \times CF \times ED \times RF\ )}$$

A shampoo use rate of 62.1 ounces per year, which is based on average shampoo use per year, was applied. The exposure duration was set equal to 70 years, which is the exposure duration required for use in Proposition 65 evaluations. The averaging time was 25,550 days, which is equivalent to 70 years. The evaluation was done using two different residue factors, 2 and 10%. The 10% percent is based on European Community Scientific Committee assumption for rinse off products. The 2% percent is based on the OEHHA assumption for the applied dose in

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shampoo that remains as a persistent residue. The resulting concentrations of coal tar that may yield exposure equal to the NSRL are 1.6×10^{-4} (0.000016 %) and 3.2×10^{-5} mg/g (0.000003 %) for the 2% and 10% absorption factors respectively. Therefore, shampoo products with coal tar concentrations above these may cause lifetime average daily exposures higher than the calculated NSRL.

There are several uncertainties that contribute to the conservative nature of the calculated NSRL.

NSRL is a value that has uncertainties associated with it. These uncertainties, which arise at every step of the characterization, are based on assumptions made typically to ensure that is result is conservative. These uncertainties are evaluated to provide an indication of the relative degree of uncertainty associated with the NSRL.

Exposure Duration

In this report, the exposure assessment is based on default Proposition 65 assumptions. The exposure duration of 70 years assumes that use of the shampoo will occur constantly and consistently for the lifespan of an individual. The assumption is very conservative and results in estimating a lower NSRL, than if shorter exposure durations were used.

Animal Study Design

The Fraunhofer (1997) study used mice as its dermal carcinogenicity model. Mice are the most sensitive laboratory model for B(a)P-induced skin cancer (EPA, 1997). The use of the mouse provides the most conservative cancer potency results for determining a NSRL.

Carcinogenic Toxicity Criteria

Uncertainty due to extrapolation of toxicological data for potential carcinogens tested in animals to human data is more prominent for potentially carcinogenic chemicals than non-carcinogenic ones. The LMS model assumes that there is no threshold for carcinogenic substances; that is, exposure to even one molecule of a carcinogen is sufficient to cause cancer. This is a highly conservative assumption because the body has several mechanisms to protect against cancer.

The use of the LMS model to extrapolate is a well-recognized source of significant uncertainty in the development of carcinogenic toxicity criteria and, subsequently, theoretical carcinogenic risk estimates. At high levels of exposure, there may indeed be a risk of cancer regardless of whether the effect occurs via a threshold mechanism or not. An animal bioassay can't determine what happens at low levels of exposure, however, which are generally typical of human exposure levels.

At low levels of exposure, the probability of cancer cannot be measured but must be extrapolated from higher dosages. To do this, animals are typically exposed to carcinogens at levels that are orders of magnitude greater than those likely to be encountered by humans in the environment. It would be difficult, if not impossible, to perform animal experiments with a large enough number of animals to directly estimate the level of risk at the low exposure levels typically encountered by humans. Thus, to estimate the risk to humans exposed at low levels, dose-response data derived from animals given high dosages are extrapolated downward using mathematical models such as the LMS, which assumes that there is no threshold of response. The dose-response curve

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generated by the model is known as the maximum likelihood estimate (MLE). The slope of the 95 percent lower confidence interval (*i.e.*, upper-bound limit) curve, which is a function of the variability in the input animal data, is taken as the CSF. CSFs are then used directly in cancer risk assessment.

The federal government, including USEPA itself, has acknowledged the limitations of the high-to-low dose extrapolation models, particularly the LMS (USEPA, 1991). In fact, this aspect of cancer risk assessment has been criticized by many scientists (including regulatory scientists) in recent years. USEPA is currently in the process of re-evaluating the 1986 cancer risk assessment guidelines (USEPA, 1996).

Several factors inherent in the LMS result in overestimated carcinogenic potency: (1) any exaggerations in the extrapolation that can be produced by some high dose responses (if they occur) are generally neglected, and (2) upper confidence limits on the actual response observed in the animal study are used rather than the actual response, resulting in upper-bound low dose extrapolations, which can greatly overestimate risk.

If you have any questions or comments, please don't hesitate to call Ken Kiefer or me at (916) 374-9050.

Sincerely,

Lee R. Shull
Principal
Health and Risk Services Program

References

Fraunhofer Institute of Toxicology. 1997. Final Report: Dermal Carcinogenicity Study of two Coal Tar Products (CTP) by Chronic Epicutaneous Application in Male CD-1 Mice.

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U.S. Environmental Protection Agency (USEPA). 1997. Draft: An Approach for Calculating Risk from Dermal Exposure to Benzo(a)pyrene Based on Point of Contact Effects.

W. D. BETTS CONSULTANCY

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ON BEHALF OF THE INTERNATIONAL TAR ASSOCIATION

//

FAX TO: **OCCUPATIONAL KNOWLEDGE INTERNATIONAL, SAN FRANCISCO, USA**

FOR THE ATTENTION OF: **MR. PERRY GOTTESFELD, EXECUTIVE DIRECTOR**

FAX NO: **00-1-415-441-5767**

FROM: **MR. W. D. BETTS**

DATE: **29TH NOVEMBER 1999**

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MESSAGE:

In reply to your query to Dr. Thoms, please find following analyses of the two oils used in the Dermal Carcinogenicity Study of two Coal Tar Products; both were obtained from high-temperature coal-tar.

Yours sincerely,

W. D. BETTS

Appendix J

Composition of the Test Substance: CTP1

BIOCHEMISCHES INSTITUT
FÜR UMWELTCARCINOGENE
Prof. Dr. G. Grimmer

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9. März 1993

Polycyclische aromatische Kohlenwasserstoffe in der Probe
Coal tar oil (1)

Stabilitätsprüfung (0.36 mg Coal tar oil/ µl Acetonlösung)
Angaben in µg/mL

	23.02. 1. Tag	26.02. 4. Tag	2.03. 8. Tag	9.03. 15. Tag
Naphthalin	44100	43600	44600	42900
Phenanthren	11324	11280	11570	11324
Anthracen	1209	1160	1120	1209
Fluoranthen	1350	1300	1360	1350
Pyren	435	408	440	435
Benzo[b]naphtho[2,1-d]thiophen	0.97	0.96	0.99	0.97
Benzo[ghi]fluoranthen + B[c]PH	1.73	1.63	1.75	1.73
Cyclopentapyren	0.39	0.38	0.40	0.39
Benz[a]anthracen	9.13	9.10	9.12	9.13
Chrysen + Triphenylen	8.95	9.00	8.97	8.95
Benzofluoranthene [b+j+k]	7.63	7.85	7.66	7.63
Benzo[e]pyren	2.83	2.91	2.84	2.83
Benzo[a]pyren	3.64	3.43	3.59	3.64
Perylen	1.28	1.22	1.29	1.28
Indeno[1,2,3-cd]pyren	1.45	1.40	1.43	1.45
Dibenz[a,h]anthracen	0.33	0.32	0.34	0.33
Benzo[ghi]perylen	1.26	1.19	1.23	1.26
Anthanthren	0.72	0.66	0.68	0.72
Coronen	0.46	0.44	0.45	0.48

Appendix K.

Composition of the Test Substance: CTP2

BIOCHEMISCHES INSTITUT
FÜR UMWELTCARCINOGENE
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Fax 04108-83028

9. März 1993

Polycyclische aromatische Kohlenwasserstoffe in der Probe Coal tar oil (2)

Stabilitätsprüfung (0.36 mg Coal tar oil/ µl Acetonlösung)
Angaben in µg/mL

	23.02. 1. Tag	26.02. 4. Tag	2.03. 8. Tag	9.03. 15. Tag
Naphthalin	8860	8700	8480	8560
Phenanthren	44200	44000	43500	43500
Anthracen	1710	1750	1680	1600
Fluoranthen	14740	14800	14800	14300
Pyren	8320	8400	8300	8160
Benzo[b]naphtho[2,1-d]thiophen	107.0	105.8	106.3	105.3
Benzo[ghi]fluoranthen + B[c]PH	55.3	53.2	54.8	55.1
Cyclopenta[pyren	14.0	14.1	12.5	13.8
Benz[a]anthracen	428.3	432.6	427.9	422.8
Chryseen + Triphenylen	393.9	389.4	398.0	392.6
Benzofluoranthene [b+j+k]	133.8	134.7	131.9	132.5
Benzo[e]pyren	87.1	86.7	86.3	86.9
Benzo[a]pyren	98.3	97.4	97.5	97.4
Perylen	15.4	14.8	14.9	14.3
Indeno[1,2,3-cd]pyren	19.9	19.5	20.0	18.9
Dibenz[a,h]anthracen	6.9	7.0	6.9	6.7
Benzo[ghi]perylen	37.4	37.5	37.8	37.2
Anthanthren	3.5	3.4	3.3	3.5
Coronen	4.9	5.0	4.8	4.7

CSTEE/98/10_ Add. 1

Dermal Carcinogenicity Study of two Coal Tar Products (CTP) by Chronic Epicutaneous Application in Male CD-1 Mice. (78 Weeks)

FINAL REPORT

Number 4 of 4 Originals

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Date:
October 1997

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Copy of the Fraunhofer ITA GLP Certificate

NIEDERSÄCHSISCHES UMWELTMINISTERIUM

Niedersächsisches Umweltministerium · Postfach 4107 · 3000 Hannover 1

Bescheinigung

Hiermit wird bestätigt, daß die Prüfungseinrichtung(en)

Certificate

It is hereby certified that the test facility(ies)

Fraunhofer-Institut für Toxikologie und Aerosolforschung

in Nikolai-Fuchs-Str. 1, 30625 Hannover
(Ort, Anschrift)

der
(Firma)

am 06. - 08. Juni 1994
(Datum)

von der für die Überwachung zuständigen Behörde über die Einhaltung der Grundsätze der Guten Laborpraxis inspiziert worden ist (sind).

Es wird hiermit bestätigt, daß folgende Prüfungen in dieser Prüfeinrichtung nach den Grundsätzen der Guten Laborpraxis durchgeführt werden.

in
(location, address)

of
(company name)

on June, 06 - 08, 1994
(date)

was (were) inspected by the competent authority regarding compliance with the Principles of Good Laboratory Practice.

It is hereby certified that studies in this test facility are conducted in compliance with the Principles of Good Laboratory Practice.

Prüfkategorien:

1 - Prüfungen zur Bestimmung der physikalischen Eigenschaften und Gehaltsbestimmungen

2 - Prüfungen zur Bestimmung der toxikologischen Eigenschaften

3 - Prüfungen zur Bestimmung der erbgutverändernden Eigenschaften (in vitro, in vivo)

5 - Prüfungen zum Verhalten in Boden, im Wasser und in der Luft, Prüfungen zur Bioakkumulation und zur Metabolisierung

8 - Analytische Untersuchungen an biologischen Materialien

NIEDERSÄCHSISCHES UMWELTMINISTERIUM

Niedersächsisches Umweltministerium
Hannover, den 1. Februar 1995
Im Auftrage
Buschhorn
(Dr. Buschhorn)

022 024 002
10.89

Statement of Study Director

Study No.: 93/11

Test Substances: COAL TAR OIL - 1 (CTP1)
COAL TAR OIL - 2 (CTP2)

Title: Dermal Carcinogenicity Study of Two Coal Tar Products (CTP) by Chronic Epicutaneous Application in Male CD-1 Mice (78 Weeks).

The study described in this report was conducted in compliance with the GLP Principles, German Chemicals Law, Appendix 1 (July 15, 1994), OECD Guideline No. 451, May 12, 1981 and EPA/TSCA (USA) Federal Register Vol. 50, No. 188, September 27, 1985, § 798.3300.

This report provides a correct and faithful record of the results obtained.

I accept the responsibility for the validity of the study.

14.10.93

Dr. rer. nat. J. Buschmann

Study Director
Fraunhofer ITA

Quality Assurance Statement

Study No.: 93/11

Test Substances: COAL TAR OIL - 1 (CTP1)
COAL TAR OIL - 2 (CTP2)

Title: Dermal Carcinogenicity Study of Two Coal Tar Products (CTP) by Chronic Epicutaneous Application in Male CD-1 Mice (78 Weeks).

The conduct of this study has been subject to periodic inspections of critical procedures relevant to the study. The findings of these inspections were promptly reported to the study director and the management of Fraunhofer ITA. The exact dates of inspections and reports are given below.

This report has been audited by the Fraunhofer ITA Quality Assurance Unit. It describes correct presentation of the procedures and methods employed during the course of the study and accurately reflects the raw data of the study.

Date of Q.A. Inspection	Report to Study Director
December 20-21, 1993	December 23, 1993
January 21, 1994	January 21, 1994
January 24, 1994	January 24, 1994
May 19-20, 1994	May 20, 1994
August 31, 1994	August 31, 1994
October 11, 1994	October 11, 1994
October 18, 1994	October 19, 1994
May 29 - June 2, 1995	June 2, 1995
March 18-21, 1996	March 21, 1996
October 18, 1996	October 18, 1996
November 26, 1996	November 28, 1996
April 28, 1997	April 28, 1997

M.B. Ketkar 14.10.97
Dr. M.B. Ketkar
Head, Quality Assurance Unit
Fraunhofer ITA

Statement of Principal Scientists

Study No.: 93/11

Test Substances: COAL TAR OIL - 1 (CTP1)
COAL TAR OIL - 2 (CTP2)

Title: Dermal Carcinogenicity Study of Two Coal Tar Products (CTP) by Chronic Epicutaneous Application in Male CD-1 Mice (78 Weeks).

We, the undersigned, hereby declare that the work was performed by us or under our supervision according to the procedures herein described and that this report provides a correct and faithful record of the results obtained.

	Date	Signature
Hematology and Clinical Chemistry: Prof. Dr. rer. nat. W. Bartsch	2.10.97	W. Bartsch
Laboratory Animal Veterinarian: Dr. med. vet. C. Dasenbrock	6.10.97	C. Dasenbrock
Pathologist: Dr. med. vet. H. Ernst	2.10.97	H. Ernst
Biostatistician: Prof. Dr. rer. nat. B. Schneider	2.10.97	[illegible]
Chemist: Dr. rer. nat. A. Preiß	2.10.97	A. Preiß

1. Summary

The test substances CTP1 (coal tar oil with low benzo(a)pyrene content) and CTP2 (coal tar oil with medium benzo(a)pyrene content) dissolved in toluene were applied epicutaneously on the clipped skin of male CD-1 mice twice a week in a 78-week study. Each compound was administered to each of three groups of 62 animals in concentrations of 1, 3, or 9 mg per animal per treatment (amounting to 156, 468, and 1404 mg at the end of the study). The control group was treated with the corresponding volume (25 µl) of the vehicle, toluene. A positive control group receiving 7.5 µg benzo(a)pyrene per treatment (amounting to a total dose of 1170 µg per animal up to the end of the study) dissolved in toluene was run concurrently.

Although these doses were chosen based on a subchronic study, treatment with the high dose of CTP2 led to persisting, suppurative ulceration of the skin with complete focal loss of the epidermis in some of the animals. Consequently, this group was terminated on nominal days 269-274, and the following groups were added: 0.1 and 0.3 mg CTP2 per animal per treatment (amounting to 16 and 47 mg at the end of the study) and 0.3 mg CTP1 per animal per treatment (amounting to 47 mg at the end of the study), and a control group, treated with the corresponding volume (25 µl) of the vehicle, toluene.

The following parameters were investigated: Body weight, liver and kidney weight (absolute and relative), red and white blood cell count and histopathology of the treated area of the skin. Special attention was paid to local effects on the application site (shaved interscapular region of the skin).

There were no clinical signs of systemic toxicity as a result of the treatment with the test or reference substances, and no differences in mean body and organ weights compared to the negative control group were found for any of the treatment groups.

Mean lifespan was significantly decreased after treatment with 9 mg CTP1 per treatment, and with 1 mg CTP2 per treatment and above. Mean lifetime in the other groups was not influenced by the treatment.

The following significant **neoplastic histopathological findings** were observed for the different compounds (all based on the number of animals showing a given finding):

CTP1:
1 solitary squamous cell carcinoma was observed in the 3 mg dose group, while 2 solitary squamous cell papillomas were seen in the 9 mg dose group. No skin tumour was observed in the 0.3 mg and 1 mg CTP1 dose groups. All these incidences were not statistically significantly different from the control group. Lifetable analysis also did not reveal a significant influence on tumour development in the high dose CTP1 (9 mg per treatment) even taking into account the

significantly shorter lifespan of the animals.

CTP2:

Increase in squamous-cell carcinomas (3 mg per treatment and above), papillomas (1 mg per treatment and above) and multiple papillomata (9 mg per treatment).

Concerning the number of tumour-bearing animals, an increase was observed in the number of animals with tumours (1 mg per treatment and above), with single tumours (1 mg per treatment and above) as well as with benign and malignant tumours (3 mg per treatment and above). There was also an increase in the total number of tumours (1 mg per treatment and above), benign and malignant tumours (3 mg per treatment and above).

no. animals	Treatment (mg/treatment)											
	Neg. Cont.&		CTP1				CTP2					BaP
		A$	0.3	1	3	9	0.1	0.3	1	3	9 §	
total	62	62	62	62	62	62	62	62	62	62	61	62
with skin tumours	1#	0	0	0	1	2	1	3	9	23	(20#)	47
% with skin tumours	2#	0	0	0	2	3	2	5	15	37	(33#)	76
with malignant skin tumours	0	0	0	0	1	0	1	1	3	16	(6)	32
% with malignant skin tumors	0	0	0	0	2	0	2	2	5	26	(10)	52
with benign skin tumors	1#	0	0	0	0	2	0	2	6	12	(16#)	27
% with benign skin tumours	2#	0	0	0	0	3	0	3	10	19	(26#)	44
with exclusively benign tumours	1#	0	0	0	0	2	0	2	6	7	(14#)	15
% with exclusively benign tumours	2#	0	0	0	0	3	0	3	10	11	(23#)	24

& solvent control

including one animal with a cavernous haemangioma

§ terminated after 274 days

$ control group of the additional study

The following significant **non-neoplastic histopathological findings** were observed for the different compounds (all based on the number of animals showing a given finding):

CTP1:
No statistically significant deviations from the control group were observed.

CTP2:
Increase in epidermal inclusion cysts and an increase in epidermal hyperplasia with cellular atypia (3 mg per treatment and above). Ulcerative dermatitis was decreased after 0.1 and 0.3 mg per treatment, but increased after 3 mg per treatment and above.

Main **clinical findings** consisted in persistent, suppurative ulceration of the skin with complete focal loss of the epidermis in some of the animals of group 08 (9 mg CTP2).

Concerning other clinical findings in the skin, the only significant findings in the number of animals showing the given finding at any time of the study were as follows:

CTP1:
Increase in ulcerated skin (suppurate) after 3 mg per treatment and above, and decrease in erythema after 9 mg per treatment.
1/62, 2/62, and 4/62 animals in the 1 mg, 3 mg, and 9 mg CTP1 groups, respectively, showed the macroscopic finding "Nodule, apparent papilloma" at any time of the study, while 1/62 animals of the 3 mg CTP1 group macroscopically showed the finding "Nodule, suspected carcinoma". No other apparent neoplasms were observed in the other groups. No statistically significant deviations from the concurrent control group were observed for any of these findings, even taking into account the significantly shorter lifespan of the animals of the 9 mg dose group.

CTP2:
Increase in nodules (apparent papillomas) after 0.3 mg per treatment and above, and in nodules (suspected carcinomas) after 3 mg per treatment. Decrease in scaly/flaky skin after 3 mg per treatment and above and increase in ulcerated skin (suppurate) after 1 mg per treatment and above, and in ulcerated skin (dry) after 3 mg per treatment and above. After 9 mg per treatment, scabby skin, scarred skin, and erythema were decreased, apparently due to the termination of this group after 274 days.
All other findings were observed in all groups and, therefore, considered vehicle- or treatment-induced but not test substance-related.

No effects of a substance treatment were observed on macroscopic findings, except an increase in dead or moribund animals with enlarged spleen and enlarged lymph nodes in all treated groups of the main study compared to control group. These effects were obviously due to infections subsequent to skin ulcerations.

2. Introduction

2.1 Objective of the Study

This investigation was carried out in order to evaluate the possible toxic and carcinogenic potential of two coal tar products following 78 weeks of local application on the skin of male CD-1 mice.
Special attention was paid to local effects on the application site (shaved interscapular region of the skin, approx. 10 % of the total body surface area).

2.2 Guidelines for the Study

This carcinogenicity study was conducted in compliance with the Principles of Good Laboratory Practice (German Chemicals Law § 19a, Appendix 1, pp. 1724 - 1732, July 25, 1994), OECD Guideline No. 451, May 12, 1981 and EPA/TSCA (USA) Federal Register Vol. 50, No. 188, September 27, 1985, § 798.3300.
Exceptions to the guidelines are stated in chapter 4.10. Note that preliminary studies performed prior to the start of the study (Fraunhofer ITA: Final Report 93/2, 13 Weeks Study, March, 1994) and the investigations (see also: Grimmer, G.: Final Report on the Characterization and Stability of Two Tar Oils, June 15, 1993) performed by the Biochemical Institute for Environmental Carcinogens, Grosshansdorf, Germany, were not subject of this study .

2.3 Selection of Animal Species

Mice are often used for toxicity and/or carcinogenicity studies, because of the economy in their use, the information available on physiology, pathology, and the susceptibility to different chemicals. Therefore, the mouse was the species of choice and the chosen strain had been previously used in such studies. Additionally, male mice have been proven to be responsive and there is no indication found of a sexual difference due to treatment. (IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Volumes 32, 33, 34, 35, 45; Lyon, France, 1984, 1985, 1989).

2.4 Study Duration

The study was started on November 29, 1993 (dosing start day = day 0) and finished on June 2, 1995 (last day of animal sacrifice). The additional study 93/11A (s. below) was started on September 19, 1994 (dosing start day = day 0) and finished on March 22, 1996 (last day of animal sacrifice).

2.5 Dose Level Selection

Cutaneous exposure of the test substance in mice was selected to simulate the route of human exposure and as a model system for induction of skin lesions.

This study was carried out on the basis of a previous dose range study over 13 weeks. The solvent, toluene, was chosen because CPT2 formed precipitations in other solvents, including acetone. Three dose levels of each test substance (1, 3, 9 mg/treatment/animal), a solvent control (toluene) and a positive control (7.5 µg toluenic Benzo(a)Pyrene [B(a)P]/treatment/animal) with 10 mice per group were tested in order to establish concentration levels for this carcinogenicity study. The following criteria were taken into consideration: body weight gain, blood cell count and hematocrit, skin irritation, liver impairment with respect to morphology and liver enzyme levels in serum. Based on the results of the previous subchronic study, the following dose levels for this study were selected:

1, 3 , and 9 mg per animal on two days per week (amounting to 156, 468, and 1404 mg at the end of the study).

This was also in compliance with experiences with similar applications of tary materials in animal studies .(IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Volumes 32, 33, 34, 35, 45; Lyon, France, 1983, 1984,1985, 1989)

The dose of the reference substance, benzo(a)pyrene, (7.5 µg per animal twice weekly, amounting to a total dose of 1170 µg per animal up to the end of the study) was chosen on the basis of comparable carcinogenicity studies of this compound found in literature (IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Volume 32; Lyon, France, 1983).

Unexpectedly, treatment with the high dose of CTP2 after approx. 180 days of treatment led to persisting, suppurative ulceration of the skin with complete focal loss of the epidermis in some of the animals. Consequently, this group was terminated on nominal days 269-274, and the following additional groups were included (filed under study number 93/11A):

0.1 and 0.3 mg CTP2 per animal on specified days (amounting to 16 and 47 mg at the end of the study) and 0.3 mg CTP1 per animal on specified days (amounting to 47 mg at the end of the study).

3. Test Substances, Reference Substance, and Vehicle

3.1 Test Substances

CTP-1

Name:	Coal tar oil with low benzo(a)pyrene content (approx. 10 µg/g)
CAS-No.:	Mixture of 84650-04-4 and/or 90640-82-7, 90640-80-5 and/or 91955-49-2, 101896-27-9, 61789-28-4
Degree of purity:	100% coal tar distillate
Specific density (20 °C):	1.06 g/cm³
Manufacturer/Supplier:	Rütgers-VfT AG, Duisburg, Germany
Storage:	Protected from light and under nitrogen at room temperature

CTP-2

Name:	Coal tar oil with medium benzo(a)pyrene content (approx. 275 µg/g)
CAS-No.:	Mixture of 84650-04-4 and/or 90640-82-7, 90640-80-5 and/or 91955-49-2, 101896-27-9, 61789-28-4
Degree of purity:	100% coal tar distillate
Specific density (20 °C):	1.1 g/cm³
Manufacturer/Supplier:	Rütgers-VfT AG, Duisburg, Germany
Storage:	Protected from light and under nitrogen at room temperature

The analysis of composition and stability in acetone of the main contents of the test substances was performed at the Biochemical Institute of Environmental Carcinogens, Grosshansdorf, Germany, and the results are given in Appendices J - K (see also: Grimmer, G.: Final Report on the Characterization and Stability of Two Tar Oils, June 15, 1993). According to an agreement with the sponsor it was stated that the stability in toluene is comparable to that in acetone.

3.2 Reference Substance

Name:	Benzo(a)pyrene (B(a)P) (Aldrich No. B1,008-0)
CAS No.:	50 - 32 - 8
LOT No.:	60460
Degree of purity:	98%
Manufacturer/Supplier:	Aldrich-Chemie GmbH & Co., Steinheim, Germany
Storage:	Dry and protected from light at room temperature

The lot-specific product information of the reference substance is given in Appendix L.

3.3 Vehicle

Name:	Toluene (Toluol reinst, Merck No. 8323)
CAS No.:	108 - 88 - 3
Degree of purity	> 99%
Manufacturer/Supplier:	E. Merck, Darmstadt, Germany
Storage:	Protected from light at room temperature

4. Test System

4.1 Animal Model

In this study, male CD-1 mice [Crl:CD^{R}-1(ICR)BR] were used. The animals, approximately 4 weeks of age, were purchased from Charles River Wiga, Sulzfeld, Germany.

4.2 Acclimatization Period

Prior to start of the treatment period, the mice were acclimated for about two weeks in animal room T1.036 and T1.043 (additional study 93/11A) of the Fraunhofer ITA. During this time the animals were observed daily and body weight was recorded. The collected data showed that the mice were in a good healthy condition and they were therefore accepted for this study.

4.3 Identification

Each animal in the study was assigned a unique individual identification number on a numbered plate of the cage. The ears of the animals were also tattooed corresponding to the identification numbers. All data collected from an animal were filed under that number. Identification labels were kept in the animal room and showed the following information: Study number, group number, species, animal number, sex, test substance, dose level, and route of administration. The identification labels were prepared in triplicate for each animal, one copy of which was kept in the animal room and the other two in the necropsy room T1-07. When an animal died or was sacrificed, the date of death was entered on the animal room copy which was attached to the death report for identification. All cage information was checked against the death report prior to sending the animal for autopsy. The second and third copies of the animal label were completed and attached to the individual necropsy report and wet tissue bottle.

4.4 Housing and Maintenance

Room No. T1-036 was reserved for the main study, and room No. T1-043 for the additional study 93/11A. Animals were individually housed in Makrolon® type II cages. Absorbent softwood (H3/4, Hahn & Co, Kronsburg, Germany), was used in the cages. Cages were changed every week or more often if necessary.
A closed formula commercial chow in pellet form identified as "1324 N specially prepared", purchased from Altromin International, Lage, Germany, was offered ad libitum as the diet for this study. Filtered tap water was offered fresh weekly in Makrolon® bottles, ad libitum.
Temperature and relative humidity were recorded continuously. The protocols form a part of the raw data. The temperature in the animal room was 22 ± 2 °C and the rel. humidity 55 ± 15%. The animal room lighting was an artificial light/dark cycle, lights on at 6.00 a.m., lights off at 6.00 p.m.

5. Conduct of the Study

5.1 Experimental Design and Randomization

The mice were randomized on a body weight basis using a computer-generated randomization program into groups with 62 male mice in each control or treatment group. After assignment to treatment groups but prior to the initiation of treatment, all groups were evaluated for homogeneity of mean body weights and variances within each group. After onset of treatment, animal 080006 turned out to be female. It was killed, and no data of this animal were included in the study.

The following study design was chosen:

ID	No.	Sex	Group Name	Treatment twice a week with 25 µl of a toluenic solution
01	62	male	Negative control (toluene) (Solvent control)	25 µl toluene per treatment
02	62	male	Positive control B(a)P	7.5 µg B(a)P
03	62	male	Low dose CTP 1	1 mg CTP1 ▲ 0.01 µg B(a)P
04	62	male	Medium dose CTP 1	3 mg CTP1 ▲ 0.03 µg B(a)P
05	62	male	High dose CTP 1	9 mg CTP1 ▲ 0.09 µg B(a)P
06	62	male	Low dose CTP 2	1 mg CTP2 ▲ 0.27 µg B(a)P
07	62	male	Medium dose CTP 2	3 mg CTP2 ▲ 0.80 µg B(a)P
08	62	male	High dose CTP 2	9 mg CTP2 ▲ 2.4 µg B(a)P

Due to the observed persisting, suppurate ulceration of the skin (s. 1.5), group 08 was terminated earlier, and the following additional groups were included (filed under study number 93/11A):

ID	No.	Sex	Group Name	Treatment twice a week with 25 µl of a toluenic solution
09	62	male	Negative control (toluene) (Solvent control)	25 µl toluene per treatment
10	62	male	Lower dose CTP 1	0.3 mg CTP1 ▲ 0.003 µg B(a)P
11	62	male	Lowest dose CTP 2	0.1 mg CTP2 ▲ 0.027 µg B(a)P
12	62	male	Lower dose CTP 2	0.3 mg CTP2 ▲ 0.080 µg B(a)P

5.2 Duration and Frequency of Treatment

Skin of mice was painted twice a week on Monday and Thursday for a period of 78 weeks. At similar times (between 7 - 10 a.m.) all animals in the study received the vehicle, respective test substance, or the reference substance solution. The application began for all animals of groups 01-08 on November 29th, 1993, and was continued until May 26th, 1995 (except group 08). In groups 09-12, application began on September 19th, 1994 and was continued until March 14th, 1996.

All animals (except those of group 08, which were sacrificed after 39 weeks, see 1.5) were sacrificed after 78 weeks, animals of groups 01-07 on May 29th through June 2nd, 1995, those of groups 09-12 on March 18th through 21st, 1996. The animals of group 08 were sacrificed on August 25 through 30, 1994.

In some animals, ulcerations of the treated area of the skin were observed. Treatment of these animals was interrupted until ulceration was over, whereafter treatment was resumed. The number of times that treatment was interrupted is reported for the individual animals in Appendix A.

5.3 Route of Application and Preparation of Test Substance Solutions

The test substance was applied onto the interscapular skin region of the mice, because a possible route of exposure to man is dermal contact, and in the comparable studies, dermal application was also selected. Once a week, the interscapular skin region was clipped by an electric razor, one day prior to the subsequent treatment. The shaved region was approx. 10 % of the total body surface area.
Treatment was performed by application of 25 µl of solution or vehicle per animal per treatment.

The solution of the test substances was freshly prepared once every two weeks by dissolving 40 mg (group 11), 120 mg (groups 10 and 12), 400 mg (groups 03 and 06), 1200 mg (groups 04 and 07), or 3600 mg (groups 05 and 08) of CTP1 or CTP2, respectively, in toluene ad 10 ml at room temperature. The reference substance [B(a)P] solution was prepared at the same time by diluting 1 ml of a stock solution (3 mg/ml) with toluene ad 10 ml. The solutions were stored in closed bottles at 18-25 °C protected from light and air by filling the bottles with nitrogen before preparing the solutions.

5.4 Control of Test Substance Solutions (Concentration Verification)

Concentration of the solutions were analyzed in regular intervals (first three dilutions all, then once at every three months) with the gaschromatographic method supplied by the sponsor. The reference substances to be detected in CTP 1 was naphthalene, in CTP 2 phenanthrene. Benzo(a)pyrene solutions were analyzed by HPLC using an external standard method.

5.5 Daily and Weekly Observations

All animals were observed in their cages twice daily (on weekends once daily). Additionally, all animals were removed from their cages once each week, and were carefully examined for abnormalities.
During the weekly observations, special attention was paid to skin lesions. The time of onset, location, dimensions, appearance and progression or regression of possible lesions were recorded.
Individual body weights were recorded weekly throughout the study by the on-line data acquisition system DATATOX, version rC.8-1.

5.6 Hematology (Differential Blood Cell Count) and Clinical Chemistry

At 12 and 18 months, a blood smear was obtained by puncture of the tail vein (after 12 months) or Vena cava caudalis (after 18 months at sacrifice) for all animals. A differential blood cell count was performed on samples of the animals in the highest dosage and the negative control group. Additionally, blood from the Vena cava caudalis was collected from 10 animals of the high dose CPT2 group and an untreated control group (made up from sentinel animals) on Day 269 during sacrifice of group 08 (see 1.5). Heparin litium salt (>7.5 IU/ml) was used as anticoagulant. Glutamic oxaloacetic transaminase (EC 2.6.1.1), glutamic pyruvic transaminase (EC 2.6.1.2), alkaline phosphatase (EC 3.1.3.1), total bilirubin, and albumin were determined.
The hematological and clinico-chemical methods are listed in Appendix I.

5.7 Necropsy and Histopathology

All animals were sacrificed by exsanguination under CO_2 anesthesia immediately after blood collection.

Each animal was subjected to necropsy. The physical condition of the animal prior to euthanasia and the examination of the internal organs were described in detail on individual autopsy protocol sheets.

In addition to the terminal body weight, the liver and kidneys from all animals were weighed (paired organs separately). Relative organ weight data were computed.

The following organs and tissues were collected from each mouse and fixed in 10% neutral buffered formalin (lungs were inflated at approximately 20 cm water pressure with formalin):

Treated area of the skin, masses and gross lesions, pituitary, tongue, eyes, Harderian glands, nasal and paranasal cavities, larynx and pharynx, thyroid and parathyroids, trachea, lungs, thymus, heart, aorta, mediastinal lymph nodes, salivary glands, submandibular lymph nodes, liver and gall bladder, spleen, kidneys, adrenals, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, urinary bladder, mesenterium and mesenterial lymph nodes, pancreas, testes, epididymes, prostate, seminal vesicles, muscle, femur including joint and bone marrow, spinal cord, brain, peripheral nerve, sternum with bone marrow, untreated area of the skin, and extraorbital lachrymal glands.

Histological examination was conducted on the treated area of the skin of all animals in all groups. Some other organs of animals that were killed as a consequence of severe skin ulceration were also observed in order to get information on potential infections caused by these ulcerations.

Tissues for histological examination were fixed at least one week in 10 % neutral buffered formalin, embedded in Paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin.

The slides were examined by light microscopy and the observations were recorded using the PLACES 2000 system, version 1.

5.8 Statistical Evaluation

Differences between groups were considered statistically significant at $p<0.05$. Body weight, organ weights (absolute and relative), hematology and clinical chemistry data were analyzed using analysis of variance (ANOVA). If the group means differed significantly by ANOVA, the means of the treated groups were compared to that of the negative control group by the two-tailed Dunnett's test. Frequency data were analysed using chi-sqare contingency table techniques and Fisher test . Survival data including terminal sacrifice were analysed by the Kaplan-Meier method (Kaplan and Meier, J. Am. Stat. Assoc 53, 457-481,1958) using the Lifetest program (SAS Institute Inc., SAS User's Guide: Statistics, Version 5 Edition. SAS Institue Inc., Cary, NC, USA, 1985). Survival rates were investigated with logrank test (Mantel, Cancer Chemother. Rep.

50, 163-170, 1966; Cox, JR. Stat. Soc. B 34, 187-220, 1972). If there was an influence on the survival, tumour free surviving was analysed with the same procedure (Kaplan and Meier, J. Am. Stat. Assoc 53, 457-481, 1958; logrank test).
Calculations were done on Microvax 3600 (SAS) and VAX 6500 (DATATOX) computers (Digital Equipment Corporation) with the operating system OpenVMS VAX, version 6.2 and the software packages DATATOX (Instem Computer Systems, Stone, Great Britain, version rC 8-1) and SAS (SAS Institute, Cary, NC, USA, version 6.08), lifetable analysis was performed on SPSS, release 7.0.
The negative control group 01 (09 for the additional groups 10-12) served as the control for all statistical comparisons.

5.9 Exceptions to the Guidelines

Exceptions to OECD Guideline No. 451 and USA/EPA/TSCA Federal Register, Vol. 50, No. 188, 27th September 1985, were as follows:

Test animals:	Only male animals were used.
Ophthalmology:	Was not performed.
Hematology:	Only differential WBC count was done.
Clinical chemistry:	Only limited parameters were investigated.
Urine analysis:	Was not performed.
Organ weights:	Of only liver and kidneys were recorded.
Food consumption data:	Were not obtained.
Histopathology:	Only the treated area of the skin was examined.
Treatment:	Was performed only twice per week, for 78 weeks, site of application was not covered after administration.
Concentration Verification:	Were performed at Fraunhofer ITA after initial analysis and stability control by the Biochemical Institute of Environmental Carcinogens, Grosshansdorf, Germany.

These exceptions were justified and accepted by the sponsor, since the objective of the study was to evaluate possible carcinogenic effects of CTP on the skin of male CD-1 mice (see p. 8).

5.10 Study Plan Amendments/Deviations

Alterations in the study plan were made as the study progressed. These alterations did not have any influence on the validity of the study. On the contrary, they improved the quality of the study.

6. Results and Discussion

6.1 Control of Test Substance Solutions

The concentrations of the test substance solutions, which were applied, were found within ± 10 % of the nominal concentration. If determined values were outside the limit, the solutions were discarded and new test substance solutions were prepared. Only the solutions which were within the limit, were used for application. The results of the chemical analysis of these solutions are shown in Table 12 and 12a.

6.2 Lifetable Analysis

Mean lifespan (Table 1, Fig. 2a-c, Appendix A1) was significantly decreased after treatment with 9 mg CTP1 per treatment, and with 1 mg CTP2 per treatment and above. Mean lifetime in the other groups was not influenced by the treatment.
Lifetable analysis also did not reveal a significant influence on tumour development in the high dose CTP1 (9 mg per treatment) even taking into account the significantly shorter lifespan of the animals (see 6.8).
No statistically significant deviations from the concurrent control group were observed for the macroscopic findings "Nodule, apparent papilloma" and "Nodule, suspected carcinoma" in the high dose CTP1, even taking into account the significantly shorter lifespan of the animals of the 9 mg dose group (see 6.3).

6.3 Clinical Observations

Data on clinical observations of the skin are reported in Table 4a-c, as well as Fig. 4a-b and 5 a-b, individual data are given in Appendix D-F. Mortality plots are shown in Fig. 2a-c. The individual fate of the animals is shown in Appendix A.
There were no clinical signs of systemic toxicity as a result of the treatment with the test or reference substances.
However, treatment with the high dose of CTP2 after approx. 180 days of treatment led to persistent, suppurative ulceration of the skin with complete focal loss of the epidermis in some of the animals. Consequently, this group was terminated on nominal days 269-274.
Concerning clinical findings of the skin, the only significant findings in the number of animals showing the given finding at any time of the study were as follows (Table 4a-b):
Benzo(a)pyrene:
Increase in nodules (apparent papillomas) and in nodules (suspected carcinomas) and decrease in alopecia and scarred skin.

CTP1:

Increase in ulcerated skin (suppurate) after 3 mg per treatment and above, and decrease in erythema after 9 mg per treatment. 1/62, 2/62, and 4/62 animals in the 1 mg, 3 mg, and 9 mg CTP1 groups, respectively, showed the macroscopic finding "Nodule, apparent papilloma" at any time of the study, while 1/62 animals of the 3 mg CTP1 group macroscopically showed the finding "Nodule, suspected carcinoma". No other apparent neoplasms were observed in the other groups. No statistically significant deviations from the concurrent control group were observed for any of these findings, even taking into account the significantly shorter lifespan of the animals of the 9 mg dose group (p=0.0775).

CTP2:

Increase in nodules (apparent papillomas) after 0.3 mg per treatment and above, and in nodules (suspected carcinomas) after 3 mg per treatment. Decrease in scaly/flaky skin after 3 mg per treatment and above and increase in ulcerated skin (suppurate) after 1 mg per treatment and above, and in ulcerated skin (dry) after 3 mg per treatment and above. After 9 mg per treatment, the number of observations of scabby skin, scarred skin, and erythema were decreased, apparently due to the termination of this group after 274 days and the occurrence of this finding in other groups mainly later during treatment period.

All other findings were observed in all groups and, therefore, considered vehicle- or treatment-induced but not test substance-related.

Note that in Table 4a-b and Fig. 4a-b the number of animals which showed the finding "Nodule, apparent papilloma" **at any time** of the study is higher compared to the number of animals showing this finding histopathologically **at the end** of the study. This difference is due to the following reasons:

1. Papillomas may regress spontaneously, especially in connection with skin ulcerations. See Appendix E for individual data for each animal.
2. The finding "Nodule, apparent papilloma" was chosen based on macroscopic findings. These may include severe (papillary) hyperplasias as well as (histological) carcinomas with an exophytic growth pattern. This is evidenced by the fact that the incidence of the macroscopic finding "Nodule, suspected carcinoma" is lower than the number of histologically determined carcinomas. In addition, focal scar tissue or abundant focal hyperkeratosis could macroscopically have been classified as "Nodule, apparent papilloma".

The first and mean onset of apparent papillomas and suspected carcinomas is shown in Table 4c. The incidence of palpable masses at other locations than the application site is summarized in Table 5. No influence of any treatment on these palpable masses was found.

6.4 Body Weight Development

The data for body weight are summarized in Table 2 and 2a, and also in Figure 1a-c. The individual data are given in Appendix B.

No statistically significant differences in mean body weights (including terminal body weights) compared to the negative control group were found for any of the treatment groups.

6.5 Hematology and Clinical Chemistry

Results are summarized in Table 6a-b. Individual data are given in Appendix G.
In the blood smears, decreased percent lymphocytes count and increased percent segmented neutrophiles count were frequently observed in all groups and at all time points investigated. Statistical significance of the differences in mean percent lymphocytes and in mean percent segmented neutrophiles compared to negative controls was found after 18 months in the positive controls and in the medium CTP2 group. Incidences of atypical cells were comparable between groups at all time points.
The investigation of total bilirubin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase, and albumin in blood from 10 animals of the high dose CPT2 group and an untreated control group on Day 269 during sacrifice of group 08 (see 1.5) revealed similar mean values for both groups, excluding an effect of the solvent and/or high dose CTP2 on the liver.

6.6 Organ Weights

The summary of the relative and absolute organ weight data is listed in Table 3 and 3a, the individual data are given in Appendix C.
No treatment-related effects were observed.

6.7 Sacrifice Data

The gross pathology findings are summarized in Table 7a-d.
No indications of systemic effects due to CTP1, CTP2, or benzo(a)pyrene treatment were observed.
No effects of a substance treatment were observed on macroscopic findings, except an increase in dead or moribund animals with enlarged spleen and enlarged lymph nodes in all treated groups of the groups 02 - 08 (main study) compared to control group 01. These effects are obviously due to infections subsequent to skin ulcerations.

6.8 Histopathology

Histopathological findings are summarized in Tables 8-11 and Fig. 3a-b with individual data shown in Appendix H.
All data are based on the number of animals showing this finding.

1. Test substance-related findings of the skin

A) Neoplasms

Neoplasms occurring in the treated area of the skin of the CTP1 and CTP2 treatment groups were solitary or multiple (≥ 2) squamous cell papillomas and squamous cell carcinomas. These tumour types were not observed in the toluene-treated negative control groups. Squamous cell carcinomas were found in 1/62 mice of the 0.1 mg and 0.3 mg CTP2 dose groups each and in 3/62, 16/62 and 6/62 of the 1 mg, 3 mg, and 9 mg CTP2 dose groups, respectively. The difference to the negative control group was statistically significant in the 3 and 9 mg CTP2 dose groups. Multiple squamous cell carcinomas were seen only in 2 mice of the 3 mg CTP2 dose group.

Squamous cell papillomas occurred in 2/62, 6/62, 12/62 and 15/61 mice of the 0.3 mg, 1 mg, 3 mg and 9 mg CTP2 dose groups, respectively. With the exception of the 0.3 mg CTP2 dose group, the difference to the negative control was statistically significant in all the other CTP2 dose groups. Two mice of both the 1 mg and 3 mg CTP2 dose groups and 7 mice of the 9 mg CTP2 dose group had multiple papillomas.

In the CTP1-treated mice, 1 solitary squamous cell carcinoma was observed in the 3 mg dose group, while 2 solitary squamous cell papillomas were seen in the 9 mg dose group. No skin tumour was observed in the 0.3 mg and 1 mg CTP1 dose groups.

The highest number of both tumour types was observed in the B(a)P-treated positive control group: 30/62 animals had squamous cell carcinomas (multiple in 5 mice) and 27/62 mice showed squamous cell papillomas (multiple in 13 mice). Furthermore, only in the positive control group additional skin tumour types could be detected which also have to be considered to be related to the B(a)P treatment. Besides 4 basal cell carcinomas and 1 benign basal cell tumour, 1 sebaceous carcinoma, 2 sebaceous adenomas, 1 malignant fibrous histiocytoma and 2 malignant schwannomas were observed.

The only neoplasm occurring in the toluene-treated negative control group was a cavernous haemangioma. This tumour type was also observed in a single mouse of the 9 mg CTP2 dose group, but is considered as an incidental finding. Infiltration of the skin by lymphoma cells was

observed in single animals of the B(a)P, 0.3 mg and 1 mg CTP1 and in the 0.3 mg and 1 mg CTP2 dose groups, respectively.

B) Non-neoplastic lesions

Focal to multifocal hyperplastic and inflammatory changes in the treated area of the skin were observed in all substance- and solvent-treated groups. Moderate to severe epidermal hyperplasia with cellular atypia was observed in 1/62 mice of the negative control group A, but occurred at statistically significant levels in the B(a)P (29/62 mice), 3 mg (11/62 mice) and 9 mg (13/62 mice) CTP2 treatment groups. This change which has to be regarded as pre-neoplastic, affected 5/62 animals of the 1 mg CTP2 dose group and between 1/62 and 2/62 mice of the 1 mg, 3 mg and 9 mg CTP1 treatment groups, respectively.

In contrast, the incidence of regular epidermal hyperplasia (without cellular atypia) was higher in the negative control groups, all CTP1 dose groups and in the 0.1 mg and 0.3 mg CTP2 groups (incidences between 60/62 and 62/62 mice) than in the B(a)P, 1 mg, 3 mg and 9 mg CTP2 dose groups (incidences between 33/62 and 56/62 mice). The grade of epidermal hyperplasia varied dose-dependently from very slight (minimal) to severe. Epidermal hyperplasia usually not only involved the surface epithelium, but also the epithelium of the hair follicles.

Individual animals of different groups (up to 2/62 per group) had basal cell hyperplasia (with cellular atypia) and sebaceous hypertrophy/hyperplasia (up to 4/62 per group) in addition to epidermal hyperplasia. Epidermal hyperplasia (with and without cellular atypia) was usually associated with very slight to severe focal or multifocal hyperkeratosis of the treated back skin (incidences between 60/62 and 62/62 mice, all groups).

Treatment-related inflammatory changes of the skin were observed in all groups and consisted either of slight to severe ulcerative dermatitis (ulceration) or (superficial) purulent dermatitis.

Ulcerative dermatitis was characterized by a focal to multifocal complete loss of the epidermis and pronounced suppurative inflammation of the underlying tissues, while (superficial) purulent dermatitis was characterized by mixed dermal and epidermal inflammatory cell infiltration, often associated with epidermal erosions. Both types of dermatitis were chronic as reflected by fibrotic

thickening of the corium which commonly also involved the subcutis. Subepidermal edema and focal hyalinization of the corium (amyloid deposits ?) were further morphological features of the induced inflammation.

The incidence of ulcerative dermatitis was significantly increased only in the 3 mg (40/62 mice) and 9mg (35/62 mice) CTP2 dose groups as compared to the negative control group (22/62 mice). In the negative control group A, the B(a)P, CTP1, 0.1 mg, 0.3 mg and 1 mg CTP2 treatment groups, between 11/62 and 32/62 animals per group were affected by ulcerative dermatitis.

(Superficial) purulent dermatitis of slight to severe degrees was observed in 9/62 to 37/62 mice of all groups with comparable or even lower incidences in the treatment groups than in the negative control groups. Slight to severe epidermal erosions were seen in 3/62 to 14/62 animals per group with no significant differences between the negative control and the treatment groups.

Epidermal keratin (inclusion) cysts of usually small size were significantly more frequent in the 3 mg (9/62 mice) and 9 mg (8/62 mice) CTP2 dose groups as compared to the corresponding negative control group (0/62 mice). The incidences of this lesion in the other groups ranged between 0/62 and 5/62 mice per group. Inclusion cysts were frequently associated with ulcerative dermatitis.

Other skin lesions such as abscesses, mast-cell infiltration and cholesterol granulomas affected only individual animals of different groups.

2. Other findings

From some animals which died or were killed at an early stage of the study, some other organs were examined in addition to the skin. Histopathological changes in these organs included pleuritis of the lung, hepatocellular necrosis, amyloidosis and abscesses of the liver, nephritis and testicular serositis. All these findings could be related to treatment of the skin and were mostly due to secondary bacterial infection of the skin lesions.

Conclusions

The following **significant neoplastic and non-neoplastic histopathological findings** were observed for the different compounds (All data are based on the number of animals showing this finding):

Benzo(a)pyrene:

There was an increase in squamous-cell carcinomas, papillomas and multiple papillomata and an increase in mice with epidermal hyperplasia with cellular atypia compared to the negative control group. Concerning the number of tumour-bearing animals, an increase was observed in the number of animals with tumours, with single and multiple tumours as well as with benign and malignant tumours. There was also an increase in the total number of tumours, benign and malignant tumours.

CTP1:

No statistically significant deviations from the control group were observed. Lifetable analysis also did not reveal a significant influence on tumour development in the high dose CTP1 (9 mg per treatment) even taking into account the significantly shorter lifespan of the animals (p=0.2363).

CTP2:

There was an increase in squamous-cell carcinomas (3 mg per treatment and above), papillomas (1 mg per treatment and above) and multiple papillomata (9 mg per treatment), an increase in mice with epidermal hyperplasia with cellular atypia (3 mg per treatment and above), and an increase in epidermal inclusion cysts (3 mg per treatment and above) compared to the concurrent negative control. Ulcerative dermatitis was decreased after 0.1 and 0.3 mg per treatment, but increased after 3 mg per treatment and above. Concerning the number of tumour-bearing animals, an increase was observed in the number of animals with tumours (1 mg per treatment and above), with single tumours (1 mg per treatment and above) as well as with benign and malignant tumours (3 mg per treatment and above). There was also an increase in

the total number of tumours (1 mg per treatment and above), benign and malignant tumours (3 mg per treatment and above).

no. animals	Treatment (mg/treatment)											
	Neg. Cont.&		CTP1				CTP2					Ba P
		A$	0.3	1	3	9	0.1	0.3	1	3	9 §	
total	62	62	62	62	62	62	62	62	62	62	61	62
with skin tumours	1#	0	0	0	1	2	1	3	9	23	(20#)	47
% with skin tumours	2#	0	0	0	2	3	2	5	15	37	(33#)	76
with malignant skin tumours	0	0	0	0	1	0	1	1	3	16	(6)	32
% with malignant skin tumors	0	0	0	0	2	0	2	2	5	26	(10)	52
with benign skin tumors	1#	0	0	0	0	2	0	2	6	12	(16#)	27
% with benign skin tumours	2#	0	0	0	0	3	0	3	10	19	(26#)	44
with exclusively benign tumours	1#	0	0	0	0	2	0	2	6	7	(14#)	15
% with exclusively benign tumours	2#	0	0	0	0	3	0	3	10	11	(23#)	24

& solvent control

including one animal with a cavernous haemangioma

§ terminated after 274 days

$ control group of the additional study

7. Tables and Figures

In the tables, the following abbreviations are generally used:

Negat. Cont.	Negative control group 01 (toluene, solvent control)
Posit. Cont.	Positive control group 02 (7.5 µg benzo(a)pyrene) per animal per application
Low CTP1	Low dose CTP1, group 03 (1 mg CTP1 per animal per application)
Medium CTP1	Medium dose CTP1, group 04 (3 mg CTP1 per animal per application)
High CTP1	High dose CTP1, group 05 (9 mg CTP1 per animal per application)
Low CTP2	Low dose CTP2, group 06 (1 mg CTP2 per animal per application)
Medium CTP2	Medium dose CTP2, group 07 (3 mg CTP2 per animal per application)
High CTP2	High dose CTP2, group 08 (9 mg CTP2 per animal per application)
Negat. Cont. A	Negative control group 09 of the additional groups (toluene)
Lower CTP1	Lower dose CTP1, group 10 (0.3 mg CTP1 per animal per application)
Lowest CTP2	Lowest dose CTP2, group 11 (0.1 mg CTP2 per animal per application)
Lower CTP2	Lower dose CTP2, group 12 (0.3 mg CTP2 per animal per application)
Anova	Analysis of variance

Table 1: Mean Lifespan of the Animals

Group	log rank (p)	Mean (days)
Negative Control	-	494
1 mg CTP1	0.1049	483
3 mg CTP1	0.0606	471
9 mg CTP1	0.0023	447
1 mg CTP2	0.0136	444
3 mg CTP2	0.0000	407
9 mg CTP2	0.0001	252
Negative Control A	-	471
0.3 mg CTP1	0.4788	493
0.1 mg CTP2	0.4685	504
0.3 mg CTP2	0.5785	473

Table 2: Body Weight (CTP1)

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

Body Weight (G)

MALES

	Negat. Cont.			Posit. Cont.			Low CTP1			Medium CTP1			High CTP1		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
DAY 1	32.2	1.7	62	32.1	1.6	62	31.8	2.0	62	32.2	1.9	62	32.5	2.1	62
DAY 8	33.1	1.8	62	33.1	1.7	62	32.7	2.2	62	33.3	2.1	62	33.5	2.2	62
DAY 15	33.8	1.9	61	34.3	1.9	62	34.1	2.2	62	34.3	2.1	62	34.5	2.3	62
DAY 22	34.7	1.9	61	34.8	2.0	62	34.4	2.3	62	34.8	2.1	62	35.2	2.3	62
DAY 29	35.3	2.0	61	35.3	2.0	62	34.9	2.2	62	35.2	2.2	62	35.6	2.3	62
DAY 36	35.6	2.0	61	35.6	2.0	62	35.3	2.2	62	35.6	2.3	62	36.1	2.4	62
DAY 43	36.3	2.1	61	36.4	2.0	62	36.2	2.3	62	36.3	2.4	62	36.9	2.4	62
DAY 50	36.6	2.2	60	36.4	2.1	62	36.5	2.3	62	36.4	2.4	62	37.3	2.3	62
DAY 57	36.8	2.1	60	37.0	2.1	62	36.9	2.5	62	36.8	2.4	62	37.5	2.4	62
DAY 64	37.2	2.1	60	37.2	2.1	62	37.4	2.6	62	37.2	2.4	62	38.1	2.5	62
DAY 71	37.6	2.3	60	37.6	2.3	62	38.0	2.7	62	37.7	2.4	62	38.5	2.4	62
DAY 78	37.9	2.3	60	37.8	2.3	62	37.9	2.8	62	37.8	2.5	62	38.6	2.5	62
DAY 85	38.2	2.3	60	38.1	2.3	62	38.1	2.8	62	38.1	2.6	62	38.8	2.5	62
DAY 92	38.4	2.2	60	38.4	2.2	62	38.3	2.8	62	38.2	2.6	62	38.8	2.5	62
DAY 120	39.1	2.6	60	38.7	2.3	62	39.0	3.1	62	38.9	2.6	62	39.5	2.7	62
DAY 148	39.5	2.7	60	39.3	2.6	62	39.6	3.3	62	39.5	2.6	62	39.6	2.9	62
DAY 176	39.5	2.7	60	39.8	2.9	62	40.4	3.3	62	40.2	2.5	61	40.3	2.9	62
DAY 204	40.5	2.9	59	40.4	2.9	62	40.6	3.5	62	40.5	2.5	61	40.7	2.9	62
DAY 232	40.9	2.7	59	40.9	3.0	62	41.3	3.5	62	40.9	2.5	59	41.1	2.9	59
DAY 260	41.3	2.6	58	41.3	3.0	62	41.4	3.5	61	41.0	2.5	57	41.6	3.0	55
DAY 288	42.0	3.0	58	41.9	3.1	61	42.1	3.4	61	41.3	2.5	55	42.1	3.3	54
DAY 316	42.0	2.8	57	42.0	3.2	59	42.0	3.6	60	41.4	2.6	55	41.8	2.9	52
DAY 344	41.8	2.7	57	42.3	3.2	58	42.5	3.8	57	41.7	2.6	53	42.0	2.9	50
DAY 372	42.0	3.1	55	42.4	3.1	54	41.9	3.8	56	41.5	2.6	52	41.9	2.9	47
DAY 400	42.0	3.2	55	42.0	2.9	50	41.9	3.7	53	41.0	3.0	49	42.1	3.0	42
DAY 428	41.8	3.0	54	42.3	3.0	47	41.7	4.1	45	41.4	2.9	44	42.2	2.9	37
DAY 456	41.9	3.2	51	43.2	3.2	38	42.1	4.4	40	41.6	3.1	43	41.7	2.6	34
DAY 484	41.8	3.6	46	43.2	3.2	34	42.4	4.5	37	41.8	3.1	39	41.9	2.4	30
DAY 512	41.2	3.8	44	43.2	3.4	29	42.5	4.5	32	41.8	3.7	34	41.8	3.1	26
DAY 540	41.6	3.9	38	43.1	3.2	25	42.3	5.2	28	41.3	3.5	28	41.5	2.8	22

Statistics: Anova + Dunnetts tests (two-sided): * P<=5% ** P<=1% (Exp.unit = Animal)

Table 2 (continued): Body Weight (CTP2)

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

Body Weight (G)

MALES

	Negat. Cont.			Posit. Cont.			Low CTP2			Medium CTP2			High CTP2		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
DAY 1	32.2	1.7	62	32.1	1.6	62	32.5	1.8	62	32.2	1.9	62	32.2	1.7	61
DAY 8	33.1	1.8	62	33.1	1.7	62	33.8	2.0	62	33.4	1.9	62	33.2	1.8	61
DAY 15	33.8	1.9	61	34.3	1.9	62	34.6	2.1	62	34.3	2.0	61	34.3	2.0	61
DAY 22	34.7	1.9	61	34.8	2.0	62	35.2	2.1	61	34.8	2.1	61	34.8	2.1	61
DAY 29	35.3	2.0	61	35.3	2.0	62	35.5	2.3	61	35.3	2.2	61	35.1	2.1	61
DAY 36	35.6	2.0	61	35.6	2.0	62	35.9	2.2	61	35.6	2.2	61	35.5	2.1	61
DAY 43	36.3	2.1	61	36.4	2.0	62	36.7	2.4	60	36.3	2.3	61	36.4	2.1	61
DAY 50	36.6	2.2	60	36.4	2.1	62	37.3	2.4	60	36.5	2.2	61	36.2	2.1	61
DAY 57	36.8	2.1	60	37.0	2.1	62	37.3	2.5	60	36.8	2.3	61	36.8	2.0	61
DAY 64	37.2	2.1	60	37.2	2.1	62	38.0	2.5	59	37.2	2.3	61	37.2	2.2	61
DAY 71	37.6	2.3	60	37.6	2.3	62	38.3	2.6	59	37.4	2.2	61	37.6	2.2	61
DAY 78	37.9	2.3	60	37.8	2.3	62	38.3	2.6	59	37.6	2.3	61	37.7	2.3	60
DAY 85	38.2	2.3	60	38.1	2.3	62	38.4	2.6	59	37.7	2.3	61	38.0	2.4	60
DAY 92	38.4	2.2	60	38.4	2.2	62	38.3	2.7	59	37.9	2.4	61	38.0	2.4	60
DAY 120	39.1	2.6	60	38.7	2.3	62	39.2	2.8	59	38.7	2.5	61	38.5	2.4	58
DAY 148	39.5	2.7	60	39.3	2.6	62	39.7	2.8	59	39.1	2.6	61	39.0	2.4	58
DAY 176	39.5	2.7	60	39.8	2.9	62	40.0	2.8	59	39.7	2.5	60	39.4	2.5	56
DAY 204	40.5	2.9	59	40.4	2.9	62	40.4	2.6	59	40.5	2.7	60	39.7	2.4	53
DAY 232	40.9	2.7	59	40.9	3.0	62	41.3	2.6	57	40.7	2.6	56	40.3	2.4	49
DAY 260	41.3	2.6	58	41.3	3.0	62	41.7	2.6	53	41.4	2.9	55	40.3	2.2	43
DAY 288	42.0	3.0	58	41.9	3.1	61	42.2	2.8	53	41.4	2.8	51	--	--	0
DAY 316	42.0	2.8	57	42.0	3.2	59	42.0	2.9	52	41.5	2.9	48	--	--	0
DAY 344	41.8	2.7	57	42.3	3.2	58	42.3	2.9	51	42.0	2.6	46	--	--	0
DAY 372	42.0	3.1	55	42.4	3.1	54	41.7	3.1	47	41.3	2.7	40	--	--	0
DAY 400	42.0	3.2	55	42.0	2.9	50	41.9	3.2	42	41.7	2.9	35	--	--	0
DAY 428	41.8	3.0	54	42.3	3.0	47	42.1	3.4	39	41.7	2.8	28	--	--	0
DAY 456	41.9	3.2	51	43.2	3.2	38	42.0	3.5	37	42.3	2.8	24	--	--	0
DAY 484	41.8	3.6	46	43.2	3.2	34	41.8	3.4	34	42.6	2.8	18	--	--	0
DAY 512	41.2	3.8	44	43.2	3.4	29	41.3	3.3	29	41.8	3.0	16	--	--	0
DAY 540	41.6	3.9	38	43.1	3.2	25	41.2	3.4	25	41.6	3.1	12	--	--	0

Statistics: Anova + Dunnetts tests (two-sided): * P<=5% ** P<=1% (Exp.unit = Animal)

Table 2a: Body Weight (Additional Groups)

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products(Additional Groups)
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11A
Species: Mouse
Sex : Male

Body Weight (G)

MALES

	Negat. Cont.			Lower CTP1			Lowest CTP2			Lower CTP2		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
DAY 1	32.5	1.8	62	32.5	1.5	62	32.6	1.6	62	32.8	1.9	62
DAY 8	34.2	1.9	61	34.4	1.7	62	34.4	1.9	62	34.7	2.2	62
DAY 15	35.0	2.1	61	35.1	1.9	62	35.0	2.0	62	35.3	2.3	62
DAY 22	35.5	2.2	61	36.0	1.9	62	35.9	2.0	62	36.4	2.2	62
DAY 29	36.3	2.2	61	37.0	1.9	62	36.4	2.0	62	37.0	2.3	62
DAY 36	36.8	2.2	61	37.2	1.9	62	36.9	2.1	62	37.5	2.5	62
DAY 43	37.2	2.2	60	37.7	2.0	62	37.5	2.0	62	37.9	2.4	62
DAY 50	37.6	2.3	60	38.3	2.0	62	37.9	2.1	62	38.5	2.7	62
DAY 57	38.0	2.3	60	38.3	1.9	61	38.1	2.1	62	38.4	2.6	62
DAY 64	38.0	2.4	60	38.4	1.9	61	38.4	2.1	62	38.7	2.7	62
DAY 71	38.0	2.3	60	38.8	2.0	60	38.4	2.1	62	38.9	2.6	62
DAY 78	38.3	2.5	60	38.8	2.0	60	38.5	2.1	62	39.0	2.6	62
DAY 85	38.7	2.5	60	39.0	2.0	60	38.8	2.1	62	39.2	2.6	62
DAY 92	38.7	2.5	60	39.1	2.1	60	38.9	2.2	62	39.3	2.6	62
DAY 120	39.7	2.7	60	40.1	2.2	60	40.0	2.6	62	40.2	2.7	62
DAY 148	40.3	3.1	57	40.8	2.6	60	40.9	2.7	62	41.0	3.1	60
DAY 176	40.9	3.2	56	41.3	2.6	60	41.4	3.1	61	41.3	3.2	60
DAY 204	40.8	3.4	55	41.4	2.7	59	41.6	3.1	61	41.5	3.2	60
DAY 232	41.5	3.5	55	42.0	2.9	58	42.2	3.3	60	41.7	3.2	58
DAY 260	42.2	3.1	54	42.7	3.0	57	42.7	3.5	60	42.3	3.2	56
DAY 288	41.7	3.2	54	42.2	3.0	56	42.3	3.4	59	42.3	3.2	54
DAY 316	42.0	3.3	53	42.5	3.0	56	42.1	3.5	58	42.4	3.1	52
DAY 344	42.7	3.4	53	43.3	3.0	56	43.4	3.6	57	43.1	3.1	52
DAY 372	42.1	3.2	52	42.7	2.8	56	42.7	3.4	57	42.8	2.8	52
DAY 400	42.5	3.3	52	42.8	3.2	55	42.7	3.4	56	42.5	2.8	50
DAY 428	42.1	3.2	52	42.7	2.8	53	42.7	3.4	54	42.8	2.7	48
DAY 456	42.2	3.6	49	42.6	3.1	49	42.7	3.3	50	43.0	2.9	46
DAY 484	42.9	3.5	45	42.8	3.0	48	42.8	3.0	47	43.2	3.1	41
DAY 512	42.7	3.4	40	42.8	3.3	45	42.5	3.4	45	43.0	3.1	35
DAY 540	42.2	3.2	33	43.1	3.2	40	42.7	3.2	38	42.7	3.6	32

Statistics: Anova + Dunnetts tests (two-sided): * P<=5% ** P<=1% (Exp.unit = Animal)

Table 3: Terminal Body Weight, Absolute and Relative Organ Weights

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

Group Means

MALES		Day 546 TermBW G	Day 546 L Kidney G	Day 546 R Kidney G	Day 546 Liver G	Day 546 relLiv g/100g	Day 546 rel lK g/100g	Day 546 rel rK g/100g
Negat. Cont.	Mean	40.4	0.432	0.466	2.321	5.73	1.07	1.16
	SD	4.0	0.086	0.092	0.445	0.84	0.24	0.30
	n	36	36	36	36	36	36	36
Posit. Cont.	Mean	41.0	0.401	0.419	2.562	6.23	0.98	1.02
	SD	3.5	0.074	0.081	1.003	2.26	0.13	0.15
	n	25	25	25	25	25	25	25
Low CTP1	Mean	40.5	0.423	0.433	2.190	5.43	1.05	1.08
	SD	4.9	0.066	0.076	0.499	1.14	0.16	0.17
	n	28	28	28	28	28	28	28
Medium CTP1	Mean	39.8	0.407	0.421	2.278	5.77	1.03	1.06
	SD	3.3	0.070	0.077	0.309	1.00	0.17	0.18
	n	26	26	26	26	26	26	26
High CTP1	Mean	39.5	0.409	0.436	2.297	5.83	1.03	1.10
	SD	2.9	0.069	0.062	0.771	1.99	0.14	0.12
	n	20	20	20	20	20	20	20
Low CTP2	Mean	39.1	0.413	0.424	2.179	5.57	1.06	1.08
	SD	3.4	0.069	0.069	0.528	1.29	0.15	0.15
	n	23	23	23	23	23	23	23
Medium CTP2	Mean	39.5	0.373	0.398	2.394	6.08	0.94	1.01
	SD	2.1	0.057	0.061	0.680	1.77	0.14	0.16
	n	11	11	11	11	11	11	11

Statistics: Anova + Dunnetts tests (two-sided): * P<=5% ** P<=1% (Exp.unit = Animal)

TermBW	Terminal body weight
L Kidney	Left kidney, absolute weight
R Kidney	Right kidney, absolute weight
Liver	Liver, absolute weight
relLiv	Liver, relative weight
rel lK	Left kidney, relative weight
rel rK	Right kidney, relative weight

Table 3 a: Terminal Body Weight, Absolute and Relative Organ Weights (Additional Groups)

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products(Additional Groups)
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11A
Species: Mouse
Sex : Male

Group Means

MALES		Day 546 TermBW G	Day 546 L Kidney G	Day 546 R Kidney G	Day 546 Liver G	Day 546 relLiv g/100g	Day 546 rel lK g/100g	Day 546 rel rK g/100g
Negat. Cont.	Mean	41.6	0.412	0.422	2.352	5.66	1.00	1.02
	SD	3.7	0.070	0.060	0.391	0.82	0.18	0.16
	n	33	33	33	33	33	33	33
Lower CTP1	Mean	41.8	0.437	0.448	2.308	5.52	1.05	1.07
	SD	2.9	0.075	0.077	0.371	0.85	0.19	0.19
	n	38	38	38	38	38	38	38
Lowest CTP2	Mean	41.9	0.418	0.438	2.367	5.65	1.00	1.05
	SD	3.9	0.083	0.063	0.543	1.20	0.17	0.14
	n	37	37	37	37	37	37	37
Lower CTP2	Mean	42.3	0.419	0.439	2.395	5.67	1.00	1.05
	SD	4.1	0.048	0.046	0.354	0.74	0.13	0.14
	n	31	31	31	31	31	31	31

Statistics: Anova + Dunnetts tests (two-sided): * P<=5% ** P<=1% (Exp.unit = Animal)

TermBW	Terminal body weight
L Kidney	Left kidney, absolute weight
R Kidney	Right kidney, absolute weight
Liver	Liver, absolute weight
relLiv	Liver, relative weight
rel lK	Left kidney, relative weight
rel rK	Right kidney, relative weight

Table 4a: Clinical Findings in the Skin: Number of animals showing the finding at any time of the study (Maximum: 62)

Dose	WNL	ALO	SCAL	SCAB	SCAR	ULC_D	ULC_S	ERYT	NOD_P	NOD_C
Neg.Cont.	62	57	61	55	52	12	8	55	1	0
Neg.Cont.A	62	58	59	49	53	11	10	54	0	0
Pos.Cont.	62	45*	61	46	37*	16	17	48	53*	19*
0.3 mg CTP1	62	59	62	44	48	11	7	51	0	0
1 mg CTP1	62	62	62	56	52	18	14	46	1	0
3 mg CTP1	62	59	61	53	54	21	23*	51	2	1
9 mg CTP1	62	60	62	48	54	21	21*	44*	4	0
Neg.Cont.	62	57	61	55	52	12	8	55	1	0
Neg.Cont.A	62	58	59	49	53	11	10	54	0	0
Pos.Cont.	62	45	61	46	37*	16	17	48	53*	19*
0.1 mg CTP2	62	56	61	40	43	8	5	49	2	1
0.3 mg CTP2	62	57	62	40	48	15	15	52	6*	1
1 mg CTP2	62	52	59	42	40	17	18*	34*	17*	1
3 mg CTP2	62	54	50*	56	49	33*	41*	49	35*	9*
9 mg CTP2 §	61	51	32*	36*	36*	26*	25*	35*	36*	0

§ terminated after 274 days
Significance of difference in a pairwise Fisher's test between concurrent control and treatment groups: *P<0.05
WNL within normal limits; ALO alopecia; SCAL scaly/flaky skin; SCAB scabby skin; SCAR scarred skin
ULC_D ulcerated skin, dry; ULC_S ulcerated skin, suppurate; ERYT erythema; NOD_P nodule, apparent papilloma; NOD_C nodule, suspected carcinoma

Table 4 b: Clinical Findings in the Skin: Percent of observations throughout the study

Dose	WNL	ALO	SCAL	SCAB	SCAR	ULC_D	ULC_S	ERYT	NOD_P	NOD_C
Neg.Cont.	45	15	30	16	8	1	1	18	0	0
Neg.Cont.A	41	23	26	14	14	1	1	26	0	0
Pos.Cont.	50	7	14	7	4	1	1	8	26	1
0.3 mg CTP1	57	15	21	10	11	1	1	13	0	0
1 mg CTP1	51	12	25	13	9	1	2	13	0	0
3 mg CTP1	46	18	24	15	11	1	2	14	2	0
9 mg CTP1	50	18	20	16	10	1	2	14	1	0
Neg.Cont.	45	15	30	16	8	1	1	18	0	0
Neg.Cont.A	41	23	26	14	14	1	1	26	0	0
Pos.Cont.	50	7	14	7	4	1	1	8	26	1
0.1 mg CTP2	64	7	21	6	6	1	1	10	1	0
0.3 mg CTP2	57	7	24	9	7	1	1	14	4	0
1 mg CTP2	64	6	13	11	7	1	3	8	6	0
3 mg CTP2	61	7	5	17	11	3	6	16	12	1
9 mg CTP2 §	61	7	4	15	10	4	5	13	11	0

§ terminated after 274 days
WNL within normal limits
ULC_D ulcerated skin, dry
ALO alopecia
ULC_S ulcerated skin, suppurate
SCAL scaly/flaky skin
ERYT erythema
SCAB scabby skin
NOD_P nodule, apparent papilloma
SCAR scarred skin
NOD_C nodule, suspected carcinoma

Table 4 c: Clinical Findings in the Skin: First Onset and Mean Onset of Nodules

	Apparent Papilloma			Suspected Carcinoma		
Dose	Incidence	First onset days	Mean onset days	Incidence	First onset days	Mean onset days
Neg.Cont.	1	512	512	–	–	–
Neg.Cont.A	–	–	–	–	–	–
Pos.Cont.	53	184	314	19	351	461
0.3 mg CTP1	–	–	–	–	–	–
1 mg CTP1	1	394	394	–	–	–
3 mg CTP1	2	240	261	1	478	478
9 mg CTP1	4	212	418	–	–	–
Neg.Cont.	1	512	512	–	–	–
Neg.Cont.A	–	–	–	–	–	–
Pos.Cont.	53	184	314	19	352	461
0.1 mg CTP2	2	345	369	1	534	534
0.3 mg CTP2	6	114	307	1	485	485
1 mg CTP2	17	121	348	1	387	387
3 mg CTP2	35	163	321	9	366	438
9 mg CTP2 §	36	72	208	–	–	–

§ terminated after 274 days

Table 5: Palpable Masses at Other Locations

Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

PALPABLE MASS INCIDENCE: Final Report

Dose Group Dose	01 Negat. Cont.	02 Posit. Cont.	03 Low CTP1	04 Medium CTP1	05 High CTP1
Incidence (%)	6(9)	7(11)	7(11)	6(9)	2(3)
No with Multiple Masses	0	0	0	0	0
Total masses	6	7	7	6	2
Mean No. Masses Per Animal	0.1	0.1	0.1	0.1	0.0
Total animals (N)	62	62	62	62	62
Mean onset (day) of all masses	321	318	342	335	310
Mean onset (week)	46	46	49	48	45
Mean onset (day) of masses present at death	383	360	342	401	310
Mean onset (week) of masses present at death	55	52	49	58	45
Deaths	62	62	62	62	62
Deaths with masses	4	5	7	4	2
Deaths with multiple masses	0	0	0	0	0

Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

PALPABLE MASS INCIDENCE: Final Report

Dose Group Dose	01 Negat. Cont.	02 Posit. Cont.	06 Low CTP2	07 Medium CTP2	08 High CTP2
Incidence (%)	6(9)	7(11)	2(3)	6(9)	2(3)
No with Multiple Masses	0	0	0	0	0
Total masses	6	7	2	6	2
Mean No. Masses Per Animal	0.1	0.1	0.0	0.1	0.0
Total animals (N)	62	62	62	62	62
Mean onset (day) of all masses	321	318	345	329	212
Mean onset (week)	46	46	50	47	31
Mean onset (day) of masses present at death	383	360	345	394	0
Mean onset (week) of masses present at death	55	52	50	57	0
Deaths	62	62	62	62	62
Deaths with masses	4	5	2	4	0
Deaths with multiple masses	0	0	0	0	0

Table 5 a: Palpable Masses at Other Locations (Additional Groups)

Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

PALPABLE MASS INCIDENCE: Final Report

Dose Group Dose	09 Negat. Cont.	10 Lower CTP1	11 Lowest CTP2	12 Lower CTP2
Incidence (%)	3(4)	1(1)	1(1)	1(1)
No with Multiple Masses	0	0	0	0
Total masses	3	1	1	1
Mean No. Masses Per Animal	0.0	0.0	0.0	0.0
Total animals (N)	62	62	62	62
Mean onset (day) of all masses	300	534	212	212
Mean onset (week)	43	77	31	31
Mean onset (day) of masses present at death	300	534	212	212
Mean onset (week) of masses present at death	43	77	31	31
Deaths	62	62	62	62
Deaths with masses	3	1	1	1
Deaths with multiple masses	0	0	0	0

Table 6a: Hematology

Fraunhofer ITA
Study : 93/11
Species: Mouse

Mean Leukocyte Differential Count

MALES		LYM %	SEGM %	BAND %	EOS %	BASO %	MONO %	NORMO %
Nominal days in study 353								
Negat. Cont.	Mean	70	28	1	1	0	0	0
	SD	11	11	1	1	0	1	0
	n	55	55	55	55	55	55	55
Posit. Cont.	Mean	69	29	1	0	0	0	0
	SD	15	14	1	1	0	1	0
	n	54	54	54	54	54	54	54
High CTP1	Mean	67	30	1	1	0	1	0
	SD	13	13	1	1	0	1	0
	n	48	48	48	48	48	48	48
Low CTP2	Mean	68	31	0	0	0	0	0
	SD	17	16	1	1	0	0	0
	n	49	49	49	49	49	49	49
Medium CTP2	Mean	66	32	0	1	0	1	0
	SD	17	16	1	1	0	1	0
	n	40	40	40	40	40	40	40
Nominal days in study 546								
Negat. Cont.	Mean	62	36	1	1	0	0	0
	SD	16	16	3	1	0	0	0
	n	36	36	36	36	36	36	36
Posit. Cont.	Mean	46*	51*	1	1	0	0	0
	SD	26	25	2	1	0	0	0
	n	25	25	25	25	25	25	25
High CTP1	Mean	62	37	0	0	0	0	0
	SD	18	18	1	1	0	0	0
	n	20	20	20	20	20	20	20
Low CTP2	Mean	59	41	0	0	0	0	0
	SD	18	17	1	1	0	0	0
	n	23	23	23	23	23	23	23
Medium CTP2	Mean	43*	56*	0	0	0	0	0
	SD	23	22	1	1	0	0	0
	n	11	11	11	11	11	11	11

Statistics: Anova + Dunnetts tests (two-sided): * P<=5% ** P<=1% (Exp.unit = Animal)

LYM = Lymphocytes
BAND = Banded Neutrophiles
BASO = Basophiles
NORMO = Nucleated red cells
SEGM = Segmented neutrophiles
EOS = Eosinophiles
MONO = Monocytes

Table 6a (continued): Hematology

Fraunhofer ITA
Study: 93/11

Differential Blood Cell Count
Nominal days in study 353

Number of Animals with Notations

GROUP		01	02	05	06	07	PROBIT
M A L E S							
LYM%	LOW	3/55	10/54	10/48	10/49	9/40	0.135
SEG%	HIGH	6/55	12/54	13/48	11/49	12/40	0.187
BAND%	HIGH	0/55	1/54	1/48	1/49	0/40	0.750
EOS%	HIGH	0/55	0/54	0/48	0/49	0/40	1.000
BASO%	HIGH	0/55	0/54	0/48	0/49	0/40	1.000
MONO%	HIGH	0/55	0/54	0/48	0/49	0/40	1.000
NORMO%	HIGH	0/55	0/54	0/48	0/49	0/40	1.000
JUV%	HIGH	0/55	0/54	0/48	0/49	0/40	1.000
MYEL%	HIGH	0/55	0/54	0/48	0/49	0/40	1.000
DIV%	HIGH	0/55	0/54	0/48	1/49	0/40	0.401
ANISO	HIGH	0/55	1/54	2/48	2/49	0/40	0.391
POIK	HIGH	0/55	0/54	1/48	0/49	0/40	0.387
HYPO	HIGH	0/55	0/54	1/48	1/49	0/40	0.542
JOLLY	HIGH	0/55	0/54	0/48	0/49	0/40	1.000

Statistics: Chi-square Contingency Tables

Table 6a (continued): Hematology

Nominal days in study 546

Number of Animals with Notations

GROUP		01	02	05	06	07	PROBIT
M A L E S							
LYM%	LOW	12/36	12/25	6/20	8/23	9/11	0.035
SEG%	HIGH	12/36	12/25	11/20	11/23	9/11	0.074
BAND%	HIGH	1/36	3/25	0/20	0/23	0/11	0.116
EOS%	HIGH	0/36	0/25	0/20	0/23	0/11	1.000
BASO%	HIGH	0/36	0/25	0/20	0/23	0/11	1.000
MONO%	HIGH	0/36	0/25	0/20	0/23	0/11	1.000
NORMO%	HIGH	0/36	0/25	0/20	0/23	0/11	1.000
JUV%	HIGH	0/36	0/25	0/20	0/23	0/11	1.000
MYEL%	HIGH	0/36	0/25	0/20	0/23	0/11	1.000
DIV%	HIGH	1/36	3/25	0/20	0/23	1/11	0.179
ANISO	HIGH	1/36	4/25	0/20	0/23	1/11	0.061
POIK	HIGH	0/36	0/25	0/20	0/23	0/11	1.000
HYPO	HIGH	0/36	1/25	0/20	0/23	0/11	0.458
JOLLY	HIGH	0/36	0/25	0/20	0/23	0/11	1.000

Statistics: Chi-square Contingency Tables

Groups: 01 = Negat. Cont.; 02 = Posit. Cont.; 05 = High CTP1; 06 = Low CTP2; 07 = Medium CTP2

Numbers below and above the ranges indicated in brackets are classified as low and high, respectively:

LYM = Lymphocytes (55-95%)
BAND = Banded Neutrophiles (0-3%)
BASO = Basophiles (0%)
NORMO = Nucleated red cells (0%)
MYEL = Myeloblasts (0%)

SEGM = Segmented neutrophiles (5-40%)
EOS = Eosinophiles (0-5%)
MONO = Monocytes (0-5%)
JUV = Metamyelocytes (0%)
DIV = Atypical cells (0%)

ANISO = Anisocyosis (0)
JOLLY = Jolly's (Howell's) bodies (0)

HYPO = Hypochromasia (0)
POIK = Poikilocytosis (0)

Table 6a (continued): Hematology

Fraunhofer ITA
Study: 93/11A

Differential Blood Cell Count
Nominal days in study 368

Number of Animals with Notations

GROUP		09	10	11	12	PROBIT
M A L E S						
LYM%	LOW	12/53	20/56	9/57	14/52	0.101
SEG%	HIGH	15/53	20/56	14/57	16/52	0.623
BAND%	HIGH	1/53	3/56	3/57	3/52	0.757
EOS%	HIGH	0/53	0/56	0/57	0/52	1.000
BASO%	HIGH	4/53	1/56	1/57	2/52	0.332
MONO%	HIGH	0/53	0/56	0/57	0/52	1.000
NORMO%	HIGH	1/53	2/56	1/57	2/52	0.865
JUV%	HIGH	0/53	2/56	0/57	1/52	0.303
MYEL%	HIGH	0/53	1/56	0/57	0/52	0.406
DIV%	HIGH	18/53	20/56	21/57	20/52	0.970
ANISO	HIGH	1/53	6/56	4/56	2/52	0.225
POIK	HIGH	2/53	6/56	4/56	2/52	0.400
JOLLY	HIGH	1/53	14/56	7/57	10/52	0.005

Statistics: Chi-square Contingency Tables

Table 6a (continued): Hematology

Nominal days in study 546

Number of Animals with Notations

GROUP		09	10	11	12	PROBIT
M A L E S						
LYM%	LOW	10/33	11/37	7/37	13/31	0.232
SEG%	HIGH	11/33	13/37	9/37	15/31	0.226
BAND%	HIGH	3/33	6/37	3/37	3/31	0.674
EOS%	HIGH	0/33	0/37	0/37	0/31	1.000
BASO%	HIGH	0/33	0/37	0/37	0/31	1.000
MONO%	HIGH	0/33	0/37	0/37	0/31	1.000
NORMO%	HIGH	1/33	0/37	0/37	2/31	0.219
JUV%	HIGH	0/33	0/37	0/37	0/31	1.000
MYEL%	HIGH	0/33	0/37	0/37	0/31	1.000
DIV%	HIGH	13/33	7/37	9/37	11/31	0.205
ANISO	HIGH	15/33	22/37	24/37	25/31	0.034
POIK	HIGH	15/33	22/37	24/37	25/31	0.034
JOLLY	HIGH	7/33	11/37	11/37	11/31	0.654

Statistics: Chi-square Contingency Tables

Groups: 09 = Negat. Cont.; 10 = Lower CTP1; 11 = Lowest CTP2; 12 = Lower CTP2

Numbers below and above the ranges indicated in brackets are classified as low and high, respectively:

LYM = Lymphocytes (55-95%)
BAND = Banded Neutrophiles (0-3%)
BASO = Basophiles (0%)
NORMO = Nucleated red cells (0%)
MYEL = Myeloblasts (0%)

SEGM = Segmented neutrophiles (5-40%)
EOS = Eosinophiles (0-5%)
MONO = Monocytes (0-5%)
JUV = Metamyelocytes (0%)
DIV = Atypical cells (0%)

ANISO = Anisocyosis (0)
POIK = Poikilocytosis (0)

JOLLY = Jolly's (Howell's) bodies (0)

Table 6b: Clinical Chemistry

Fraunhofer ITA
Study : 93/11
Species: Mouse

Mean Clinical Chemistry

Nominal days in study 269

MALES		T.BILI umol/l	GOT U/l	GPT U/l	AP U/l	ALB g/l
High CTP2	Mean	3.8	29	34	76	31.3
	SD	2.1	12	22	20	1.5
	n	10	10	10	10	10
Control	Mean	2.8	32	37	72	30.4
	SD	0.8	9	16	12	2.0
	n	10	10	10	10	10

Statistics: Anova * P<=5% ** P<=1% (Exp.unit = Animal)

T.BILI = Total Bilirubin
GPT = Glutamic Pyruvic Transaminase
ALB = Albumin
GOT = Glutamic Oxaloacetic Transaminase
AP = Alkaline Phosphatase

Control group made up from untreated sentinel animals

Table 7a: Macroscopic Findings: Terminal Sacrifice

Group	01	02	03	04	05	06	07	08
n	36	25	28	26	20	23	11	40
Extraorb. lacrimal glands: enlarged	1	-	-	-	-	-	-	-
white/yellow/brown coloured	1	-	1	-	-	1	-	-
firm consistency	1	-	-	-	-	-	-	-
Ear: red/scabby	1	-	3	-	2	-	-	-
Lower jaw: nodule	-	-	-	-	-	-	-	-
Eyelids/Eyes: red/cataracts	3	3	2	3	2	1	-	-
S.c. oedema	1	1	-	-	-	-	-	-
Thyroid gland: enlarged	1	1	1	2	-	-	-	-
Submandibular LN: enlarged/white	3	2	2	1	2	3	-	5
firm consistency	1	2	2	-	-	1	-	-
Salivary glands: enlarged	-	-	-	-	-	1	-	-
firm consistency	1	2	1	2	3	1	-	5
Thymus: brown/red/yellow	-	-	-	1	-	-	-	-
other findings	-	-	-	-	-	-	-	-
Heart: discoloured areas	2	2	2	3	-	3	-	-
other findings	-	-	-	-	1	-	-	-
Heart Atrium: enlarged	2	2	1	3	-	1	-	-
firm consistency	2	1	-	2	-	-	-	-
dark red/yellow	1	-	-	1	-	1	-	-
other findings	-	1	-	-	-	-	-	-
Lung: red/dark red	3	2	3	1	3	3	1	-
pink/yellow	8	10	2	4	3	2	2	1
pink/red spots	18	7	15	19	7	12	7	31
nodules	3	5	4	2	1	5	1	-
glassy/lardaceous/discoloured areas	7	6	7	4	6	6	1	3
other findings	2	3	1	2	1	1	-	2
LALN: enlarged	1	1	2	-	1	1	-	2
yellow/brown	-	1	1	-	1	-	-	1
Liver: lobulated	1	-	3	2	1	2	2	5
brown/light brown/red	3	4	4	4	2	3	1	2
raised/discoloured areas	3	3	3	2	1	1	1	-

Table 7 a(continued): Macroscopic Findings: Terminal Sacrifice

Group	01	02	03	04	05	06	07	08
n	36	25	28	26	20	23	11	40
Liver: nodules	-	1	1	1	-	2	-	1
other findings	-	4	2	1	2	1	2	7
Spleen: enlarged	5	11	1	3	4	2	1	8
discoloured	1	1	-	-	1	1	-	-
discoloured areas/cysts	3	8	3	3	2	2	1	-
other findings	3	5	1	3	1	-	1	3
Adrenals: discoloured/areas	-	-	-	1	-	-	-	-
Kidneys: cysts	6	6	6	4	5	5	2	-
enlarged	5	1	3	2	-	-	1	-
furrowed/granular/humpy surface	7	-	2	3	3	1	1	-
yellow/light brown	11	2	6	3	7	7	3	-
brown/yellow areas	4	1	2	3	2	1	1	1
other findings	1	-	1	1	-	-	-	-
Bladder: white concrements	-	-	1	-	-	1	-	-
distended	2	3	-	-	1	-	-	1
Ureter: dilated	2	-	2	1	2	4	-	-
Mesenterial LN.: enlarged	1	1	2	-	1	2	1	5
Body LN: enlarged	4	7	2	2	3	1	2	3
Stomach: distended	-	-	-	-	-	-	-	-
surface changes	4	4	3	1	4	3	-	8
Intestinal tract: distended/discoloured	-	-	-	-	-	1	1	-
Gall bladder: enlarged	1	-	-	-	-	-	1	-
Pancreas: white/grey areas	-	2	2	1	1	2	-	-
oedema	1	1	2	-	-	-	1	-
Testes: reduced size	3	2	1	4	1	2	-	3
other findings	1	2	1	2	-	1	-	-
Seminal vesicles: enlarged	20	11	18	12	12	13	5	-
white/brown	29	22	25	18	16	22	10	-
firm consistency	8	6	7	4	7	3	1	-
Preputial glands: enlarged	-	-	1	2	1	-	-	-
Tail: nodules	1	-	-	-	-	-	-	-

Table 7 b: Macroscopic Findings: Dead / Moribund Animals

Group	01	02	03	04	05	06	07	08
n	26	37	34	36	42	39	51	21
Extraorb. lacrimal glands: enlarged	-	-	-	-	-	-	-	-
white/yellow/brown coloured	1	1	1	3	2	2	2	-
firm consistency	1	1	-	2	-	-	-	-
Ear: red/scabby	-	-	1	2	1	2	2	-
Lower jaw: nodule	2	1	-	-	1	1	-	-
Eyelids/Eyes: red/cataracts	1	2	4	6	3	2	-	-
S.c. oedema	4	9	2	1	6	7	5	2
Thyroid gland: enlarged	-	2	1	2	-	-	-	-
Submandibular LN: enlarged/white	7	10	12	14	15	16	21	9
firm consistency	1	1	1	-	-	2	4	2
Salivary glands: enlarged	1	-	-	1	1	2	3	3
firm consistency	4	9	6	10	13	10	16	7
Thymus: brown/red/yellow	4	-	-	-	-	1	1	-
other findings	2	1	1	-	-	1	1	-
Heart: discoloured areas	9	5	8	10	6	5	1	2
other findings	1	1	-	-	-	-	4	1
Heart Atrium: enlarged	4	6	4	8	9	4	1	-
firm consistency	1	4	-	6	7	4	-	-
dark red/yellow	4	8	3	5	10	5	1	-
other findings	-	-	-	-	-	-	-	-
Lung: red/dark red	4	3	4	3	8	5	1	1
pink/yellow	7	13	6	6	11	8	15	5
pink/red spots	9	16	16	15	20	14	25	9
nodules	1	4	1	3	1	-	-	-
glassy/lardaceous/discoloured areas	4	9	4	6	5	7	9	4
other findings	3	2	3	7	9	3	4	2
LALN: enlarged	1	4	3	6	4	5	7	2
yellow/brown	-	1	-	-	1	-	2	2
Liver: lobulated	5	2	4	4	5	3	7	6
brown/light brown/red	7	6	4	7	8	10	14	4
raised/discoloured areas	2	3	3	4	9	10	10	11

Table 7 b(continued): Macroscopic Findings: Dead / Moribund Animals

Group	01	02	03	04	05	06	07	08
n	26	37	34	36	42	39	51	21
Liver: nodules	1	1	1	2	-	1	2	1
other findings	7	5	15	11	14	11	28	13
Spleen: enlarged	9	24	17	22	21	20	39	16
discoloured	-	2	3	4	3	2	4	-
discoloured areas/cysts	4	12	7	8	4	5	12	-
other findings	2	3	4	6	9	5	13	2
Adrenals: discoloured/areas	-	2	2	4	1	2	2	2
Kidneys: cysts	-	3	1	2	3	1	1	-
enlarged	2	3	2	4	2	4	4	1
furrowed/granular/humpy surface	2	1	1	4	8	6	5	1
yellow/light brown	7	9	12	10	12	11	15	3
brown/yellow areas	2	2	4	7	5	7	5	7
other findings	-	3	2	-	2	2	3	-
Bladder: white concrements	-	1	1	-	1	-	-	-
distended	1	4	3	2	3	1	3	1
Ureter: dilated	1	3	2	2	2	-	1	-
Mesenterial LN.: enlarged	1	9	2	4	4	5	6	3
Body LN: enlarged	3	11	12	14	16	14	24	13
Stomach: distended	2	1	-	-	4	1	1	-
surface changes	11	10	11	15	11	13	15	7
Intestinal tract: distended/discoloured	1	5	6	2	5	5	3	-
Gall bladder: enlarged	1	3	-	1	1	2	-	-
Pancreas: white/grey areas	3	3	2	4	3	4	3	-
oedema	5	6	4	3	7	5	2	-
Testes: reduced size	6	6	5	6	4	7	13	2
other findings	1	2	1	3	3	1	5	-
Seminal vesicles: enlarged	12	12	10	14	9	10	9	-
white/brown	12	10	11	14	9	8	8	-
firm consistency	6	6	5	8	6	6	3	-
Preputial glands: enlarged	1	-	1	-	-	1	-	-
Tail: nodules	-	3	-	1	-	-	1	-

Table 7 c: Macroscopic Findings: Terminal Sacrifice (Additional Groups)

Group	09	10	11	12
n	33	35	37	31
Extraorb. lacrimal glands: enlarged	-	-	-	-
white/yellow/brown coloured	-	-	-	-
firm consistency	-	-	-	-
Ear: red/scabby	-	-	-	1
Lower jaw: nodule	-	-	-	-
Eyelids/Eyes: red/cataracts	3	2	1	1
S.c. oedema	3	-	2	1
Thyroid gland: enlarged	-	-	-	-
Submandibular LN: enlarged/white	2	-	2	3
firm consistency	1	-	-	4
Salivary glands: enlarged	1	2	-	-
firm consistency	-	5	4	-
Thymus: brown/red/yellow	1	-	-	-
other findings	-	-	-	-
Heart: discoloured areas	1	1	1	1
other findings	-	-	4	1
Heart Atrium: enlarged	1	-	1	2
firm consistency	-	-	2	1
dark red/yellow	1	-	2	3
other findings	-	-	-	-
Lung: red/dark red	3	4	5	6
pink/yellow	2	3	1	1
pink/red spots	13	10	11	14
nodules	2	6	7	5
glassy/lardaceous/discoloured areas	2	4	4	1
other findings	1	3	2	2
LALN: enlarged	2	1	3	1
yellow/brown	-	-	-	1
Liver: lobulated	-	-	-	-
brown/light brown/red	-	1	1	-
raised/discoloured areas	4	2	1	3

Table 7 c(continued): Macroscopic Findings: Terminal Sacrifice (Additional Groups)

Group	09	10	11	12
n	33	35	37	31
Liver: nodules	3	4	1	1
other findings	1	-	2	3
Spleen: enlarged	3	3	1	3
discoloured	1	-	2	-
discoloured areas/cysts	-	1	1	-
other findings	2	2	-	-
Adrenals: discoloured/areas	-	-	-	-
Kidneys: cysts	5	6	4	3
enlarged	1	2	2	1
furrowed/granular/humpy surface	2	3	5	3
yellow/light brown	2	5	4	3
brown/yellow areas	7	6	2	2
other findings	-	2	-	-
Bladder: white concrements	-	-	-	-
distended	-	-	-	-
Ureter: dilated	-	1	-	-
Mesenterial LN.: enlarged	7	4	6	4
Body LN: enlarged	7	1	2	3
Stomach: distended	-	-	-	-
surface changes	1	5	4	2
Intestinal tract: distended/discoloured	1	-	-	-
Gall bladder: enlarged	-	-	1	-
Pancreas: white/grey areas	1	1	2	-
oedema	2	3	3	2
Testes: reduced size	1	-	-	-
other findings	2	1	-	1
Seminal vesicles: enlarged	8	12	17	11
white/brown	7	9	11	4
firm consistency	-	1	-	-
Preputial glands: enlarged	1	-	-	-
Tail: nodules	-	-	-	-

Table 7 d: Macroscopic Findings: Dead / Moribund Animals (Additional Groups)

Gruppe	09	10	11	12
n	29	27	25	31
Extraorb. lacrimal glands:	-	-	-	-
white/yellow/brown coloured	-	-	-	-
firm consistency	-	-	-	-
Ear: red/scabby	1	1	-	2
Lower jaw: nodule	-	-	1	1
Eyelids/Eyes: red/cataracts	-	3	1	3
S.c. oedema	2	5	5	4
Thyroid gland: enlarged	-	1	2	1
Submandibular LN: enlar-	6	9	4	7
firm consistency	2	2	1	-
Salivary glands: enlarged	3	2	2	-
firm consistency	3	4	3	-
Thymus: brown/red/yellow	1	-	1	-
other findings	2	1	-	-
Heart: discoloured areas	1	-	4	5
other findings	3	4	3	4
Heart Atrium: enlarged	2	5	4	5
firm consistency	1	-	2	3
dark red/yellow	1	2	2	3
other findings	1	1	2	4
Lung: red/dark red	7	4	6	7
pink/yellow	9	3	4	6
pink/red spots	14	12	10	12
nodules	1	1	1	1
glassy/lardaceous/discoloured	6	1	6	3
other findings	4	1	1	1
LALN: enlarged	1	3	5	7
yellow/brown	-	-	1	-
Liver: lobulated	3	2	2	2
brown/light brown/red	3	2	5	2
rasised/discoloured areas	2	-	3	4

Table 7 d(continued): Macroscopic Findings: Dead / Moribund Animals (Additional Groups)

Gruppe	09	10	11	12
n	29	27	25	31
Liver: nodules	1	2	-	1
other findings	3	6	7	8
Spleen: enlarged	11	13	11	12
discoloured	2	2	-	2
discoloured areas/cysts	2	7	8	2
other findings	-	2	3	3
Adrenals: discoloured/areas	1	-	-	-
Kidneys: cysts	-	1	1	1
enlarged	-	-	2	2
furrowed/granular/humpy sur-	4	2	3	3
yellow/light brown	3	2	8	5
brown/yellow areas	1	2	3	5
other findings	1	-	-	-
Bladder: white concrements	-	-	2	-
distended	1	1	-	4
Ureter: dilated	-	-	1	4
Mesenterial LN.: enlarged	7	6	6	3
Body LN: enlarged	9	11	7	9
Stomach: distended	1	-	-	1
surface changes	9	10	5	8
Intestinal tract: disten-	3	1	1	2
Gall bladder: enlarged	2	-	5	-
Pancreas: white/grey areas	1	-	2	2
oedema	3	3	8	2
Testes: reduced size	2	-	1	1
other findings	2	1	-	3
Seminal vesicles: enlarged	7	7	4	9
white/brown	14	11	10	11
firm consistency	2	2	1	1
Preputial glands: enlarged	-	-	2	1
Tail: nodules	-	-	-	-

Table 8: Summary of Histopathological findings

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
		Tolue.	B(a)P	1 mg CTP 1	3 mg CTP 1	9 mg CTP 1	1 mg CTP 2	3 mg CTP 2	9 mg CTP 2
LUNGS		(1)				(1)			(2)
No abnormality detected		1 (100%)				1 (100%)			1 (50%)
Pleuritis		0 (0%)				0 (0%)			1 (50%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
		Tolue.	B(a)P	1 mg CTP 1	3 mg CTP 1	9 mg CTP 1	1 mg CTP 2	3 mg CTP 2	9 mg CTP 2
LIVER		(1)			(3)	(2)	(1)	(1)	(5)
Hepatocellular necrosis		1 (100%)			0 (0%)	1 (50%)	1 (100%)	1 (100%)	3 (60%)
Amyloidosis		1 (100%)			2 (67%)	2 (100%)	1 (100%)	1 (100%)	5 (100%)
Abscesses		1 (100%)			3 (100%)	2 (100%)	1 (100%)	0 (0%)	5 (100%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 8 (continued): Summary of Histopathological findings

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings

LESIONS	INCIDENCE OF LESIONS (ANIMAL REFERENCES)							
	Males							
TREATMENT	Tolue.	B(a)P	11 mg CTP 1	13 mg CTP 1	19 mg CTP 1	11 mg CTP 2	13 mg CTP 2	19 mg CTP 2
KIDNEYS								
Nephritis							(1) 1 (100%)	(2) 2 (100%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings

LESIONS	INCIDENCE OF LESIONS (ANIMAL REFERENCES)							
	Males							
TREATMENT	Tolue.	B(a)P	11 mg CTP 1	13 mg CTP 1	19 mg CTP 1	11 mg CTP 2	13 mg CTP 2	19 mg CTP 2
TESTES								
Serositis							(1) 1 (100%)	

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 8 (continued): Summary of Histopathological findings

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings

LESIONS	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
TREATMENT	Tolue.	B(a)P	1 mg CTP 1	3 mg CTP 1	9 mg CTP 1	1 mg CTP 2	3 mg CTP 2	9 mg CTP 2
SKIN	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(61)
SQUAMOUS-CELL CARCINOMA(TA) [M]	0 (0%)	30*** (48%)	0 (0%)	1 (2%)	0 (0%)	3 (5%)	16*** (26%)	6* (10%)
PAPILLOMA(TA) [B]	0 (0%)	27*** (44%)	0 (0%)	0 (0%)	2 (3%)	6* (10%)	12*** (19%)	15*** (24%)
BASAL-CELL CARCINOMA [M]	0 (0%)	4 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BASAL CELL TUMOR, BENIGN [B]	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SEBACEOUS CARCINOMA [M]	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SEBACEOUS ADENOMA [B]	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SCHWANNOMA [M]	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MALIGNANT FIBROUS HISTIOCYTOMA [M]	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cavernous HAEMANGIOMA [B]	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Infiltrated by lymphoma/leukaemic cells	0 (0%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Epidermal hyperplasia with cellular atypia	0 (0%)	29*** (47%)	2 (3%)	1 (2%)	2 (3%)	5 (8%)	11*** (18%)	13*** (21%)
Epidermal hyperplasia	62 (100%)	33*** (53%)	60 (97%)	61 (98%)	60 (97%)	56* (90%)	49*** (79%)	48*** (79%)
Hyperkeratosis	61 (98%)	61 (98%)	62 (100%)	62 (100%)	62 (100%)	61 (98%)	60 (97%)	60 (98%)
Basal-cell hyperplasia with cellular atypia	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Sebaceous hypertrophy/hyperplasia	1 (2%)	2 (3%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Ulcerative dermatitis (ulceration)	22 (35%)	19 (31%)	21 (34%)	28 (45%)	31 (50%)	21 (34%)	40** (65%)	35* (56%)
(Superficial) purulent dermatitis	25 (40%)	9** (15%)	24 (39%)	30 (48%)	27 (44%)	29 (47%)	11** (18%)	22 (36%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *p<0.05, **p<0.01, ***p<0.001
[B] Benign tumour
[M] Malignant tumour
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 8 (continued): Summary of Histopathological findings

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
		Tolue.	B(a)P	11 mg CTP 1	13 mg CTP 1	19 mg CTP 1	11 mg CTP 2	13 mg CTP 2	19 mg CTP 2
SKIN		(62)	(62)	(62)	(62)	(62)	(62)	(62)	(61)
Epidermal erosion(s)		8 (13%)	3 (5%)	12 (19%)	9 (15%)	14 (23%)	10 (16%)	4 (6%)	6 (10%)
Abscess(es)		1 (2%)	0 (0%)	1 (2%)	2 (3%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Epidermal inclusion cyst(s)		0 (0%)	2 (3%)	1 (2%)	2 (3%)	1 (2%)	5 (8%)	9** (15%)	8** (13%)
Mast-cell infiltration		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Cholesterol granuloma(ta)		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 8 (continued): Summary of Histopathological findings

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
		Tolue.	B(a)P	1 mg CTP 1	3 mg CTP 1	9 mg CTP 1	1 mg CTP 2	3 mg CTP 2	9 mg CTP 2
HAEMATOP./LYMPHORET.TISSUE			(1)	(1)			(1)		
LYMPHOMA [M]			1 (100%)	1 (100%)			1 (100%)		

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
[M] Malignant tumour
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified
*** Listing Complete ***

Table 8 a: Summary of Histopathological findings (Additional Groups)

FRAUNHOFER ITA 93/11A_CTP

Summary of histopathological findings

LESIONS	INCIDENCE OF LESIONS (ANIMA			
	Males			
TREATMENT	Tolue.	0.3 mg CTP 1	0.1 mg CTP 2	0.3 mg CTP 2
SKIN	(62)	(62)	(62)	(62)
SQUAMOUS-CELL CARCINOMA [M]	0 (0%)	0 (0%)	1 (2%)	1 (2%)
PAPILLOMA [B]	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Infiltrated by lymphoma/leukaemic cells	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Epidermal hyperplasia with cellular atypia	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Epidermal hyperplasia	61 (98%)	62 (100%)	61 (98%)	61 (98%)
Hyperkeratosis	62 (100%)	62 (100%)	62 (100%)	62 (100%)
Sebaceous hypertrophy/hyperplasia	4 (6%)	1 (2%)	2 (3%)	0 (0%)
Ulcerative dermatitis (ulceration)	32 (52%)	23 (37%)	11*** (18%)	17** (27%)
(Superficial) purulent dermatitis	27 (44%)	31 (50%)	37 (60%)	30 (48%)
Epidermal erosion(s)	9 (15%)	9 (15%)	9 (15%)	3 (5%)
Epidermal inclusion cyst(s)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Mast-cell infiltration	0 (0%)	0 (0%)	0 (0%)	1 (2%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
[B] Benign tumour
[M] Malignant tumour
Figures in brackets represent the number of animals from which this tissue was examined microscopically .
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 8 a (continued): Summary of Histopathological findings (Additional Groups)

FRAUNHOFER ITA 93/11A_CTP

Summary of histopathological findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMA		
		Males		
		Tolue.	0.3 mg CTP 1	0.1 mg CTP 2	0.3 mg CTP 2
HAEMATOP./LYMPHORET.TISSUE					
			(1)		(1)
LYMPHOMA [M]			1 (100%)		1 (100%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
[M] Malignant tumour
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Listing Complete ***

Table 9: Summary of Histopathological findings (With Score Expansions)

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
		Tolue.	B(a)P	11 mg CTP 1	13 mg CTP 1	19 mg CTP 1	11 mg CTP 2	13 mg CTP 2	19 mg CTP 2
LUNGS		(1)				(1)			(2)
No abnormality detected		1 (100%)				1 (100%)			1 (50%)
Pleuritis									
slight		0 (0%)				0 (0%)			1 (50%)
Score Expanded Totals		0 (0%)				0 (0%)			1 (50%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
		Tolue.	B(a)P	11 mg CTP 1	13 mg CTP 1	19 mg CTP 1	11 mg CTP 2	13 mg CTP 2	19 mg CTP 2
LIVER		(1)			(3)	(2)	(1)	(1)	(5)
Hepatocellular necrosis									
severe		1 (100%)			0 (0%)	1 (50%)	1 (100%)	1 (100%)	3 (60%)
Score Expanded Totals		1 (100%)			0 (0%)	1 (50%)	1 (100%)	1 (100%)	3 (60%)
Amyloidosis									
slight		1 (100%)			0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
moderate		0 (0%)			1 (33%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)
severe		0 (0%)			1 (33%)	0 (0%)	1 (100%)	0 (0%)	5 (100%)
Score Expanded Totals		1 (100%)			2 (67%)	2 (100%)	1 (100%)	1 (100%)	5 (100%)
Abscesses		1 (100%)			3 (100%)	2 (100%)	1 (100%)	0 (0%)	5 (100%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 9 (continued): Summary of Histopathological findings (With Score Expansions)

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings (with score expansion)

LESIONS	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
TREATMENT	Tolue.	B(a)P	1 mg CTP 1	3 mg CTP 1	9 mg CTP 1	1 mg CTP 2	3 mg CTP 2	9 mg CTP 2
KIDNEYS							(1)	(2)
Nephritis								
moderate							1 (100%)	0 (0%)
severe							0 (0%)	2 (100%)
Score Expanded Totals							1 (100%)	2 (100%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings (with score expansion)

LESIONS	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
TREATMENT	Tolue.	B(a)P	1 mg CTP 1	3 mg CTP 1	9 mg CTP 1	1 mg CTP 2	3 mg CTP 2	9 mg CTP 2
TESTES							(1)	
Serositis								
severe							1 (100%)	
Score Expanded Totals							1 (100%)	

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 9 (continued): Summary of Histopathological findings (With Score Expansions)

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
		Tolue.	B(a)P	11 mg CTP 1	13 mg CTP 1	19 mg CTP 1	11 mg CTP 2	13 mg CTP 2	19 mg CTP 2
SKIN		(62)	(62)	(62)	(62)	(62)	(62)	(62)	(61)
SQUAMOUS-CELL CARCINOMA(TA) [M]		0 (0%)	30*** (48%)	0 (0%)	1 (2%)	0 (0%)	3 (5%)	16*** (26%)	6* (10%)
PAPILLOMA(TA) [B]		0 (0%)	27*** (44%)	0 (0%)	0 (0%)	2 (3%)	6* (10%)	12*** (19%)	15*** (24%)
BASAL-CELL CARCINOMA [M]		0 (0%)	4 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BASAL CELL TUMOR, BENIGN [B]		0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SEBACEOUS CARCINOMA [M]		0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SEBACEOUS ADENOMA [B]		0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SCHWANNOMA [M]		0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MALIGNANT FIBROUS HISTIOCYTOMA [M]		0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cavernous HAEMANGIOMA [B]		1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Infiltrated by lymphoma/leukaemic cells		0 (0%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Epidermal hyperplasia with cellular atypia									
moderate		0 (0%)	3 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
severe		0 (0%)	26*** (42%)	2 (3%)	1 (2%)	2 (3%)	5 (8%)	10** (16%)	13*** (21%)
Score Expanded Totals		0 (0%)	29*** (47%)	2 (3%)	1 (2%)	2 (3%)	5 (8%)	11*** (18%)	13*** (21%)
Epidermal hyperplasia									
very slight		2 (3%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)
slight		28 (45%)	3*** (5%)	22 (35%)	26 (42%)	20 (32%)	20 (32%)	7*** (11%)	6*** (10%)
moderate		28 (45%)	21 (34%)	26 (42%)	23 (37%)	25 (40%)	25 (40%)	22 (35%)	22 (35%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
[B] Benign tumour
[M] Malignant tumour
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 9 (continued): Summary of Histopathological findings (With Score Expansions)

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings (with score expansion)

LESIONS	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
TREATMENT	Tolue.	B(a)P	1 mg CTP 1	3 mg CTP 1	9 mg CTP 1	1 mg CTP 2	3 mg CTP 2	9 mg CTP 2
SKIN	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(61)
Epidermal hyperplasia								
severe	4 (6%)	9 (15%)	10 (16%)	12 (19%)	15* (24%)	10 (16%)	19*** (31%)	20*** (32%)
Score Expanded Totals	62 (100%)	33*** (53%)	60 (97%)	61 (98%)	60 (97%)	56* (90%)	49*** (79%)	49*** (79%)
Hyperkeratosis								
very slight	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
slight	39 (63%)	6*** (10%)	32 (52%)	26* (42%)	16*** (26%)	23** (37%)	12*** (19%)	9*** (15%)
moderate	22 (35%)	36* (58%)	21 (34%)	31 (50%)	35* (56%)	29 (47%)	30 (48%)	36* (58%)
severe	0 (0%)	19*** (31%)	8** (13%)	5 (8%)	11*** (18%)	9** (15%)	18*** (29%)	15*** (24%)
Score Expanded Totals	61 (98%)	61 (98%)	62 (100%)	62 (100%)	62 (100%)	61 (98%)	60 (97%)	61 (98%)
Basal-cell hyperplasia with cellular atypia								
severe	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Score Expanded Totals	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Sebaceous hypertrophy/hyperplasia								
slight	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
moderate	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
severe	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals	1 (2%)	2 (3%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Ulcerative dermatitis (ulceration)								
slight	16 (26%)	2*** (3%)	3** (5%)	6* (10%)	7 (11%)	2*** (3%)	6* (10%)	7 (11%)
moderate	5 (8%)	4 (6%)	6 (10%)	6 (10%)	7 (11%)	6 (10%)	3 (5%)	6 (10%)
severe	1 (2%)	13** (21%)	12** (19%)	16*** (26%)	17*** (27%)	13** (21%)	31*** (50%)	22*** (35%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01;***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 9 (continued): Summary of Histopathological findings (With Score Expansions)

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
		Tolue.	B(a)P	11 mg CTP 1	13 mg CTP 1	19 mg CTP 1	11 mg CTP 2	13 mg CTP 2	19 mg CTP 2
SKIN		(62)	(62)	(62)	(62)	(62)	(62)	(62)	(61)
Ulcerative dermatitis (ulceration) Score Expanded Totals		22 (35%)	19 (31%)	21 (34%)	28 (45%)	31 (50%)	21 (34%)	40** (65%)	35* (56%)
(Superficial) purulent dermatitis slight		22 (35%)	7** (11%)	22 (35%)	29 (47%)	24 (39%)	26 (42%)	6*** (10%)	16 (26%)
moderate		2 (3%)	2 (3%)	2 (3%)	1 (2%)	2 (3%)	3 (5%)	5 (8%)	6 (10%)
severe		1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		25 (40%)	9** (15%)	24 (39%)	30 (48%)	27 (44%)	29 (47%)	11* (18%)	23 (37%)
Epidermal erosion(s) slight		5 (8%)	2 (3%)	6 (10%)	5 (8%)	12 (19%)	5 (8%)	3 (5%)	2 (3%)
moderate		3 (5%)	1 (2%)	5 (8%)	4 (6%)	2 (3%)	5 (8%)	1 (2%)	4 (6%)
severe		0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		8 (13%)	3 (5%)	12 (19%)	9 (15%)	14 (23%)	10 (16%)	4 (6%)	6 (10%)
Abscess(es)		1 (2%)	0 (0%)	1 (2%)	2 (3%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Epidermal inclusion cyst(s)		0 (0%)	2 (3%)	1 (2%)	2 (3%)	1 (2%)	5 (8%)	9** (15%)	8** (13%)
Mast-cell infiltration severe		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Score Expanded Totals		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Cholesterol granuloma(ta)		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 9 (continued): Summary of Histopathological findings (With Score Expansions)

FRAUNHOFER ITA 93/11_CTP

Summary of histopathological findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMAL REFERENCES) Males							
		Tolue.	B(a)P	1 mg CTP 1	3 mg CTP 1	9 mg CTP 1	1 mg CTP 2	3 mg CTP 2	9 mg CTP 2
HAEMATOP./LYMPHORET.TISSUE			(1)	(1)			(1)		
LYMPHOMA [M]			1 (100%)	1 (100%)			1 (100%)		

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
[M] Malignant tumour
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Listing Complete ***

Table 9 a: Summary of Histopathological findings (Additional Groups, With Score Expansions)

FRAUNHOFER ITA 93/11A_CTP

Summary of histopathological findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMA			
		Males			
		Tolue.	0.3 mg CTP 1	0.1 mg CTP 2	0.3 mg CTP 2
SKIN		(62)	(62)	(62)	(62)
SQUAMOUS-CELL CARCINOMA [M]		0 (0%)	0 (0%)	1 (2%)	1 (2%)
PAPILLOMA [B]		0 (0%)	0 (0%)	0 (0%)	2 (3%)
Infiltrated by lymphoma/leukaemic cells		0 (0%)	1 (2%)	0 (0%)	1 (2%)
Epidermal hyperplasia with cellular atypia					
severe		1 (2%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		1 (2%)	0 (0%)	0 (0%)	0 (0%)
Epidermal hyperplasia					
slight		22 (35%)	30 (48%)	42*** (68%)	37** (60%)
moderate		29 (47%)	23 (37%)	14** (23%)	20 (32%)
severe		10 (16%)	9 (15%)	5 (8%)	4 (6%)
Score Expanded Totals		61 (98%)	62 (100%)	61 (98%)	61 (98%)
Hyperkeratosis					
slight		23 (37%)	33 (53%)	44*** (71%)	44*** (71%)
moderate		34 (55%)	25 (40%)	15*** (24%)	17** (27%)
severe		5 (8%)	4 (6%)	3 (5%)	1 (2%)
Score Expanded Totals		62 (100%)	62 (100%)	62 (100%)	62 (100%)
Sebaceous hypertrophy/hyperplasia					
slight		3 (5%)	0 (0%)	0 (0%)	0 (0%)
moderate		1 (2%)	1 (2%)	2 (3%)	0 (0%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
[B] Benign tumour
[M] Malignant tumour
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 9 a (continued): Summary of Histopathological findings (Additional Groups, With Score Expansions)

FRAUNHOFER ITA 93/11A_CTP

Summary of histopathological findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMA			
		Males			
		Tolue.	0.3 mg CTP 1	0.1 mg CTP 2	0.3 mg CTP 2
SKIN		(62)	(62)	(62)	(62)
Sebaceous hypertrophy/hyperplasia					
Score Expanded Totals		4 (6%)	1 (2%)	2 (3%)	0 (0%)
Ulcerative dermatitis (ulceration)					
slight		14 (23%)	8 (13%)	4* (6%)	5* (8%)
moderate		8 (13%)	8 (13%)	2 (3%)	6 (10%)
severe		10 (16%)	7 (11%)	5 (8%)	6 (10%)
Score Expanded Totals		32 (52%)	23 (37%)	11*** (18%)	17* (27%)
(Superficial) purulent dermatitis					
slight		24 (39%)	29 (47%)	33 (53%)	30 (48%)
moderate		3 (5%)	2 (3%)	3 (5%)	0 (0%)
severe		0 (0%)	0 (0%)	1 (2%)	0 (0%)
Score Expanded Totals		27 (44%)	31 (50%)	37 (60%)	30 (48%)
Epidermal erosion(s)					
slight		2 (3%)	4 (6%)	5 (8%)	3 (5%)
moderate		6 (10%)	4 (6%)	3 (5%)	0* (0%)
severe		1 (2%)	1 (2%)	1 (2%)	0 (0%)
Score Expanded Totals		9 (15%)	9 (15%)	9 (15%)	3 (5%)
Epidermal inclusion cyst(s)		0 (0%)	1 (2%)	0 (0%)	1 (2%)
Mast-cell infiltration					
severe		0 (0%)	0 (0%)	0 (0%)	1 (2%)
Score Expanded Totals		0 (0%)	0 (0%)	0 (0%)	1 (2%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 9 a (continued): Summary of Histopathological findings (Additional Groups, With Score Expansions)

FRAUNHOFER ITA 93/11A_CTP

Summary of histopathological findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (ANIMA		
		Males		
		Toluo.	0.3 mg CTP 1	0.1 mg CTP 2	0.3 mg CTP 2
HAEMATOP./LYMPHORET.TISSUE			(1)		(1)
LYMPHOMA [M]			1 (100%)		1 (100%)

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
[M] Malignant tumour
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified.

*** Listing Complete ***

Table 10: Tumour Incidence by Organ

FRAUNHOFER ITA 93/11_CTP

Tumour incidence by organ

LESIONS	INCIDENCE OF TUMOURS (NUMERIC) Males							
TREATMENT	Tolue.	B(a)P	11 mg CTP 1	13 mg CTP 1	19 mg CTP 1	11 mg CTP 2	13 mg CTP 2	19 mg CTP 2
SKIN	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(61)
Multiple SQUAMOUS-CELL CARCINOMATA [M]	0	5	0	0	0	0	2	0
SQUAMOUS-CELL CARCINOMA [M]	0	25***	0	1	0	3	14***	6*
Multiple PAPILLOMATA [B]	0	13***	0	0	0	2	2	7*
PAPILLOMA [B]	0	14***	0	0	2	4	10**	8**
BASAL-CELL CARCINOMA [M]	0	4	0	0	0	0	0	0
BASAL CELL TUMOR, BENIGN [B]	0	1	0	0	0	0	0	0
SEBACEOUS CARCINOMA [M]	0	1	0	0	0	0	0	0
SEBACEOUS ADENOMA [B]	0	2	0	0	0	0	0	0
MALIGNANT FIBROUS HISTIOCYTOMA [M]	0	1	0	0	0	0	0	0
SCHWANNOMA [M]	0	2	0	0	0	0	0	0
Cavernous HAEMANGIOMA [B]	1	0	0	0	0	0	0	1
HAEMATOP./LYMPHORET.TISSUE		(1)	(1)			(1)		
LYMPHOMA [M]		1	1			1		

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
[B] Benign tumour
[M] Malignant tumour
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified
In this table, a benign tumour is ignored if a malignant tumour of the same histogenetic origin is also present in the sa

*** Listing Complete ***

Table 10 a: Tumour Incidence by Organ (Additional Groups)

FRAUNHOFER ITA 93/11A_CTP

Tumour incidence by organ

LESIONS	TREATMENT	INCIDENCE OF TUMOURS (NUMER			
		Males			
		Tolue.	0.3 mg CTP 1	0.1 mg CTP 2	0.3 mg CTP 2
SKIN		(62)	(62)	(62)	(62)
SQUAMOUS-CELL CARCINOMA [M]		0	0	1	1
PAPILLOMA [B]		0	0	0	2
HAEMATOP./LYMPHORET.TISSUE			(1)		(1)
LYMPHOMA [M]			1		1

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05,**P<0.01,***P<0.001
[B] Benign tumour
[M] Malignant tumour
Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified
In this table, a benign tumour is ignored if a malignant tumour of the same histogenetic origin is also present in the sa
*** Listing Complete ***

Table 11: Tumours of the Skin

FRAUNHOFER ITA 93/11_CTP

Tumours of the skin

LESIONS	TUMOUR TABLE							
	Males							
TREATMENT	Tolue.	B(a)P	1 mg CTP 1	3 mg CTP 1	9 mg CTP 1	1 mg CTP 2	3 mg CTP 2	9 mg CTP 2
NUMBER OF ANIMALS	62	62	62	62	62	62	62	61
NUMBER OF ANIMALS WITH TUMOURS	1	47*		1	2	9*	23*	20*
NUMBER OF ANIMALS WITH SINGLE TUMOURS	1	29*		1	2	9*	18*	18*
NUMBER OF ANIMALS WITH MULTIPLE TUMOURS		18*					5	2
NUMBER OF ANIMALS WITH BENIGN TUMOURS	1	27*			2	6	12*	16*
NUMBER OF ANIMALS WITH MALIGNANT TUMOURS		32*		1		3	16*	6*
NUMBER OF ANIMALS WITH METASTASISING TUMOURS								
TOTAL NUMBER OF TUMOURS	1	68*		1	2	9*	28*	22*
TOTAL NUMBER BENIGN TUMOURS	1	30*			2	6	12*	16*
TOTAL NUMBER OF MALIGNANT TUMOURS		38*		1		3	16*	6*
TOTAL NUMBER OF METASTASISING TUMOURS								
% ANIMALS WITH TUMOURS	2	76		2	3	15	37	32
% ANIMALS WITH SINGLE TUMOURS	2	47		2	3	15	29	29
% ANIMALS WITH MULTIPLE TUMOURS		29					8	3
% ANIMALS WITH BENIGN TUMOURS	2	44			3	10	19	26
% ANIMALS WITH MALIGNANT TUMOURS		52		2		5	26	10
% ANIMALS WITH METASTASISING TUMOURS								

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05

FRAUNHOFER ITA 93/11A_CTP

Tumours of the skin

LESIONS	TUMOUR TABLE			
	Males			
TREATMENT	Tolue.	0.3 mg CTP 1	0.1 mg CTP 2	0.3 mg CTP 2
NUMBER OF ANIMALS	62	62	62	62
NUMBER OF ANIMALS WITH TUMOURS			1	3
NUMBER OF ANIMALS WITH SINGLE TUMOURS			1	3
NUMBER OF ANIMALS WITH MULTIPLE TUMOURS				
NUMBER OF ANIMALS WITH BENIGN TUMOURS		1		2
NUMBER OF ANIMALS WITH MALIGNANT TUMOURS			1	1
NUMBER OF ANIMALS WITH METASTASISING TUMOURS				
TOTAL NUMBER OF TUMOURS			1	3
TOTAL NUMBER BENIGN TUMOURS				2
TOTAL NUMBER OF MALIGNANT TUMOURS			1	1
TOTAL NUMBER OF METASTASISING TUMOURS				
% ANIMALS WITH TUMOURS			2	5
% ANIMALS WITH SINGLE TUMOURS			2	5
% ANIMALS WITH MULTIPLE TUMOURS				
% ANIMALS WITH BENIGN TUMOURS				3
% ANIMALS WITH MALIGNANT TUMOURS			2	2
% ANIMALS WITH METASTASISING TUMOURS				

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05

Table 12: Substance Concentration (mg/ml) in the Prepared Solutions (Dose Verification)

Date of Preparation	Treatment Group						
	02	03	04	05	06	07	08
Nominal Conc. (mg/ml)	0.300	40	120	360	40	120	360
November 23rd, 1993	0.294	39.17	119.48	371.61	39.89	114.62	342.58
December 6th, 1993	0.305	39.19	122.07	362.02	36.40	113.99	346.33
December 20th, 1993		37.91	121.86	364.11	37.98	116.60	337.17
December 22nd, 1993	0.293						
February 14th, 1994	0.304						
March 14th, 1994			120.05	363.59		108.78	339.37
March 15th, 1994		40.60			37.26		
April 11th, 1994		38.51			36.72		
July 4th, 1994	0.276	36.36	118.56	347.83	38.21	116.80	357.97
October 10th, 1994		38.24	116.88	348.40	40.85	108.25	
October 24th, 1994	0.287						
January 16th, 1995	0.289	41.16	120.74	353.28	40.25	120.09	
April 10th, 1995	0.281	38.71	121.78	367.39			
April 11th, 1995					36.21	109.29	
Mean	0.291	38.87	120.18	359.78	38.20	113.55	344.68
SD	0.010	1.42	1.82	8.87	1.75	4.36	8.19
N	8	9	8	8	9	8	5

Table 12 a: Substance Concentration (mg/ml) in the Prepared Solutions of the Additional Groups (Dose Verification)

Date of Preparation	Treatment Group		
	10	11	12
Nominal Conc. (mg/ml)	12	4	12
September 12th, 1994	11.76	4.08	12.58
September 26th, 1994	11.66	4.21	12.71
October 10th, 1994	11.87	4.16	11.88
January 16th, 1995	12.08	4.17	12.04
April 11th, 1995	12.64	3.92	11.76
July 3rd, 1995	11.69	3.81	11.97
October 23rd, 1995	12.15	4.13	12.51
January 29th, 1996	12.59	3.68	12.12
Mean	12.06	4.02	12.20
SD	0.39	0.19	0.35
N	8	8	8

Figure 1a:

Body Weight: CTP1

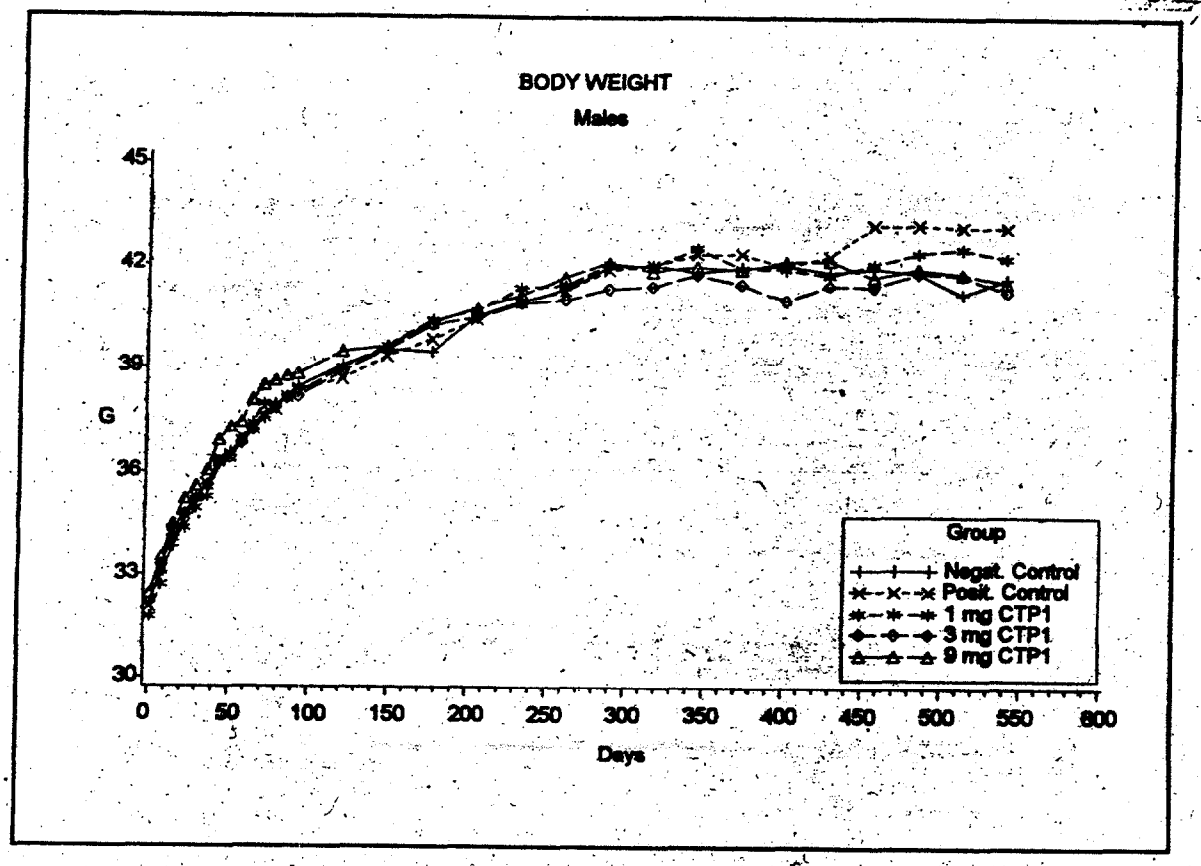


Figure 1 b:

Body Weight: CTP2

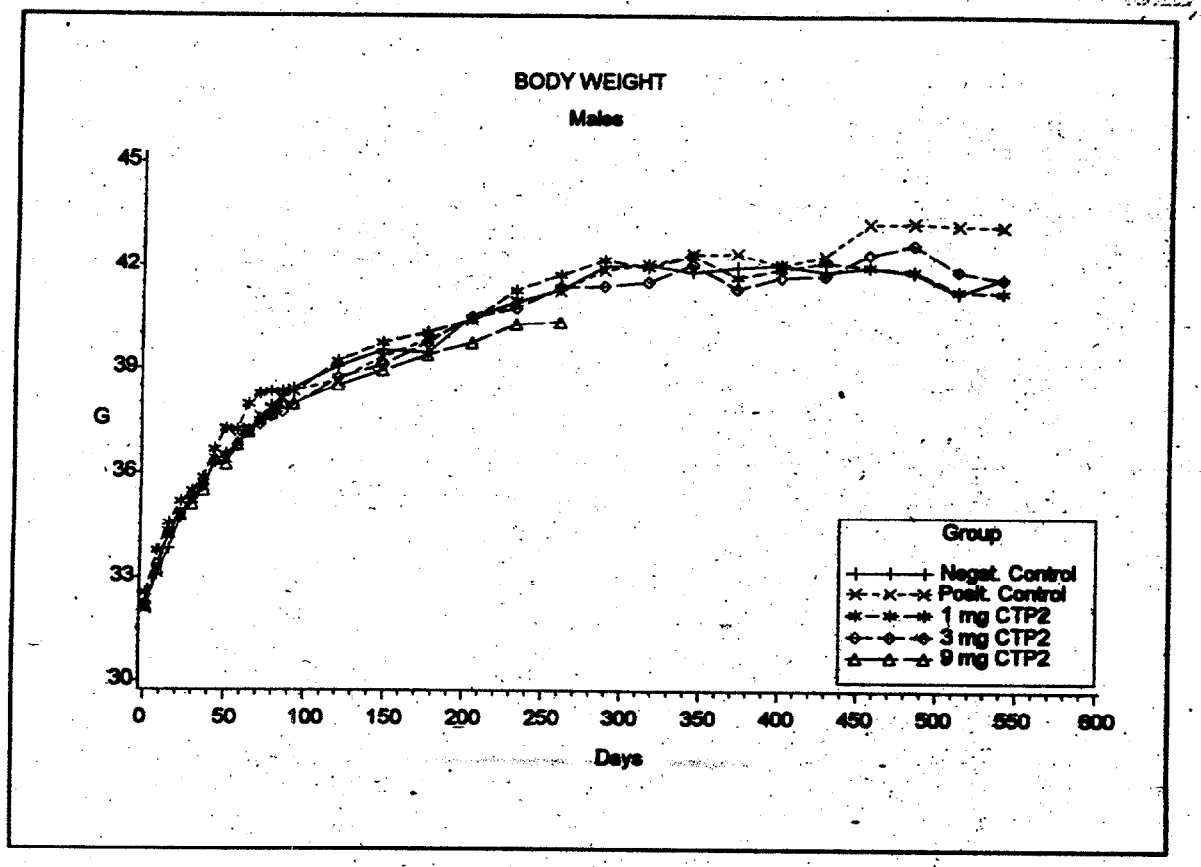


Figure 1 c:

Body Weight: Additional Groups

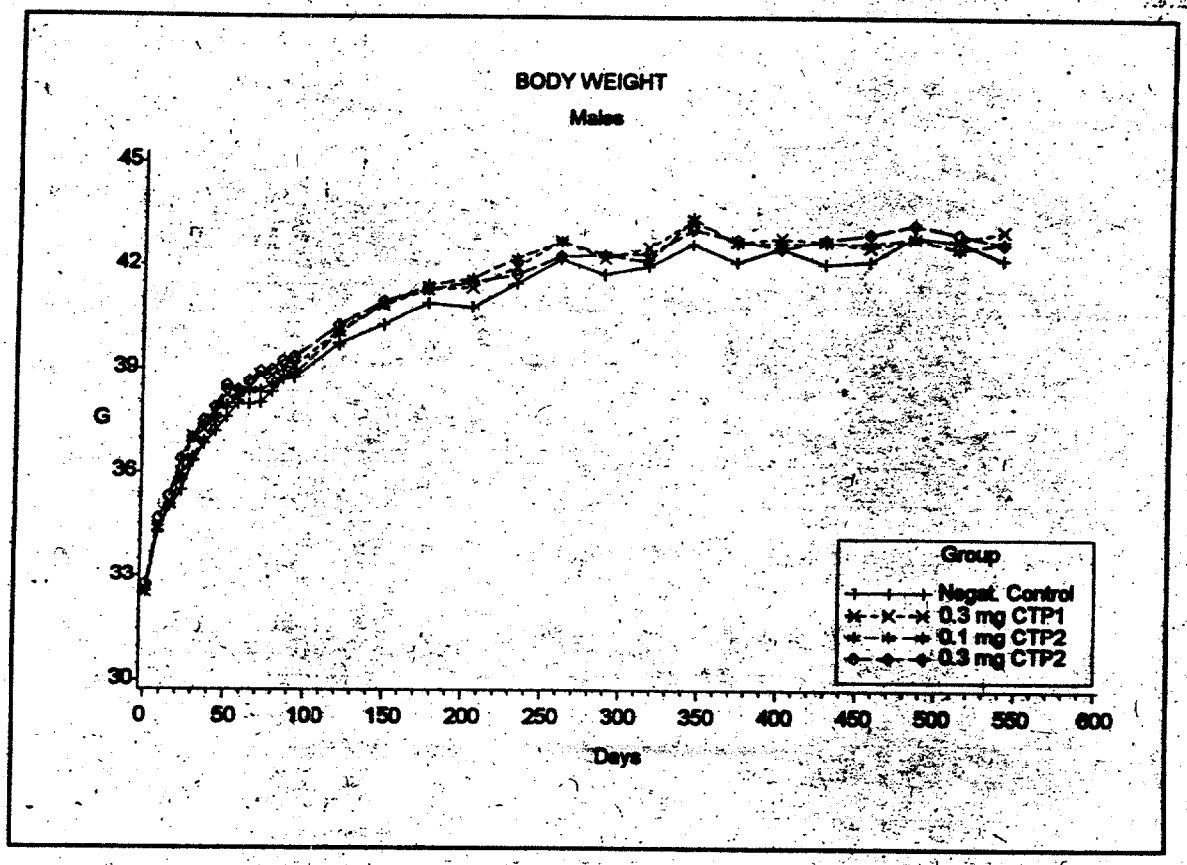


Figure 2a:

Survival Function: CTP1

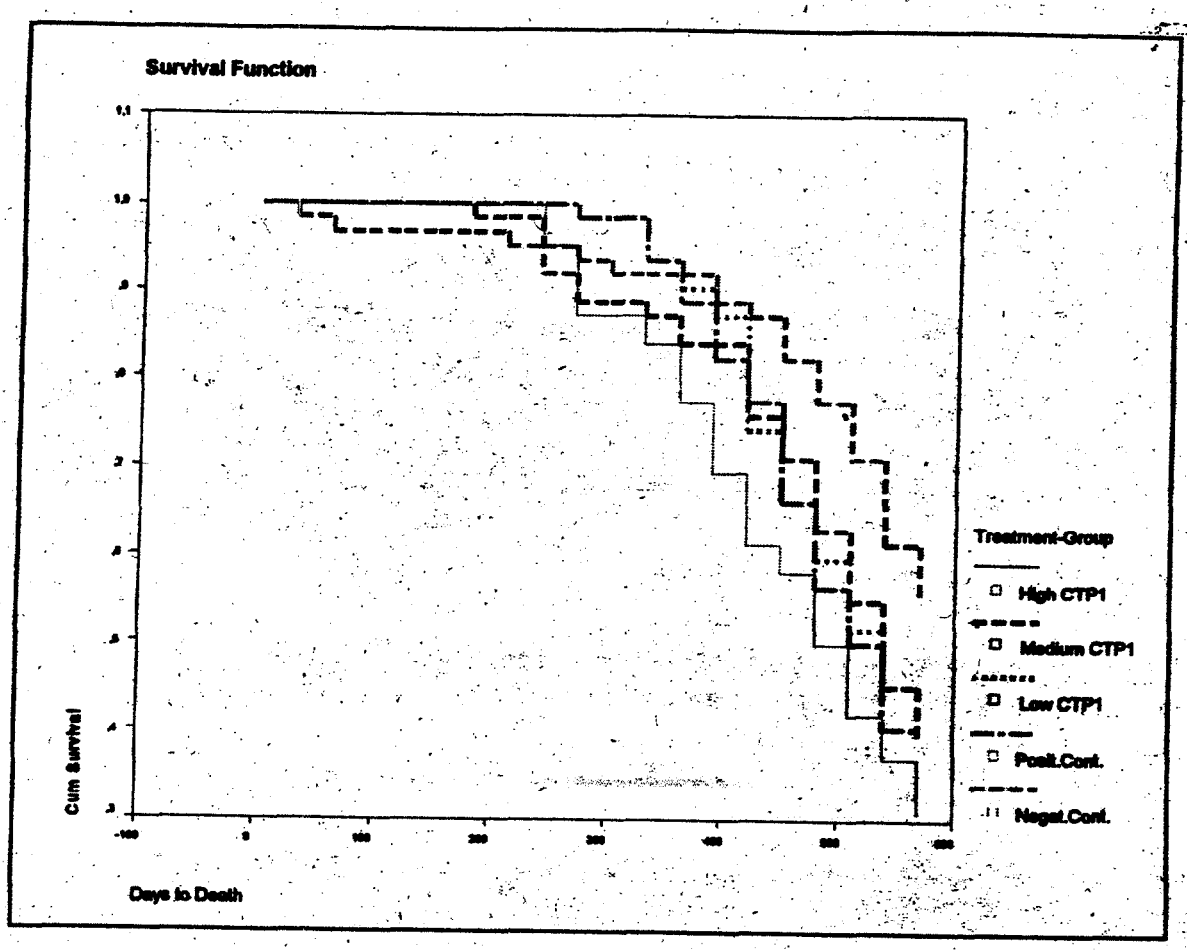


Figure 2 b:

Survival Function: CTP2

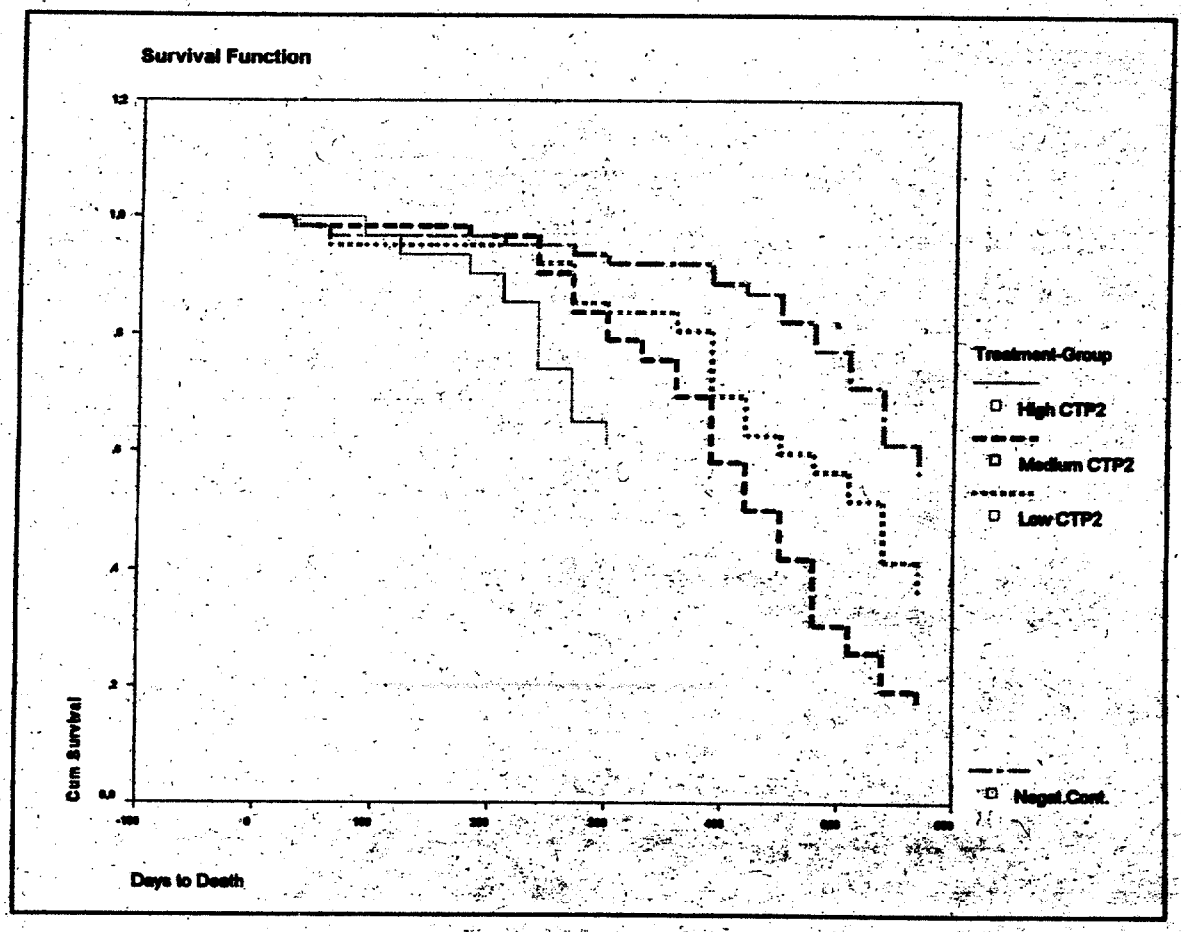


Figure 2 c:

Survival Function: Additional Groups

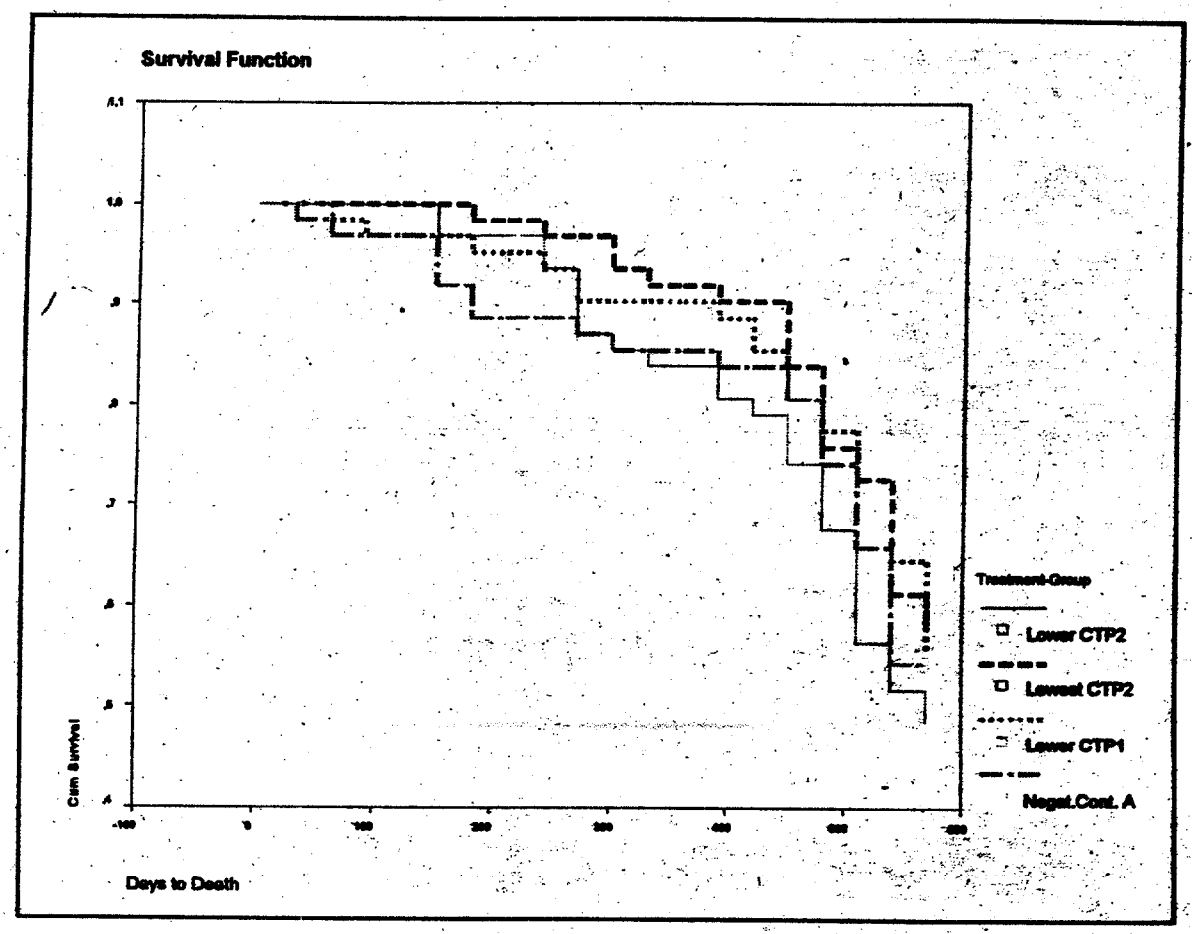


Figure 2 d:

Macroscopic Tumour Free Survival: CTP1

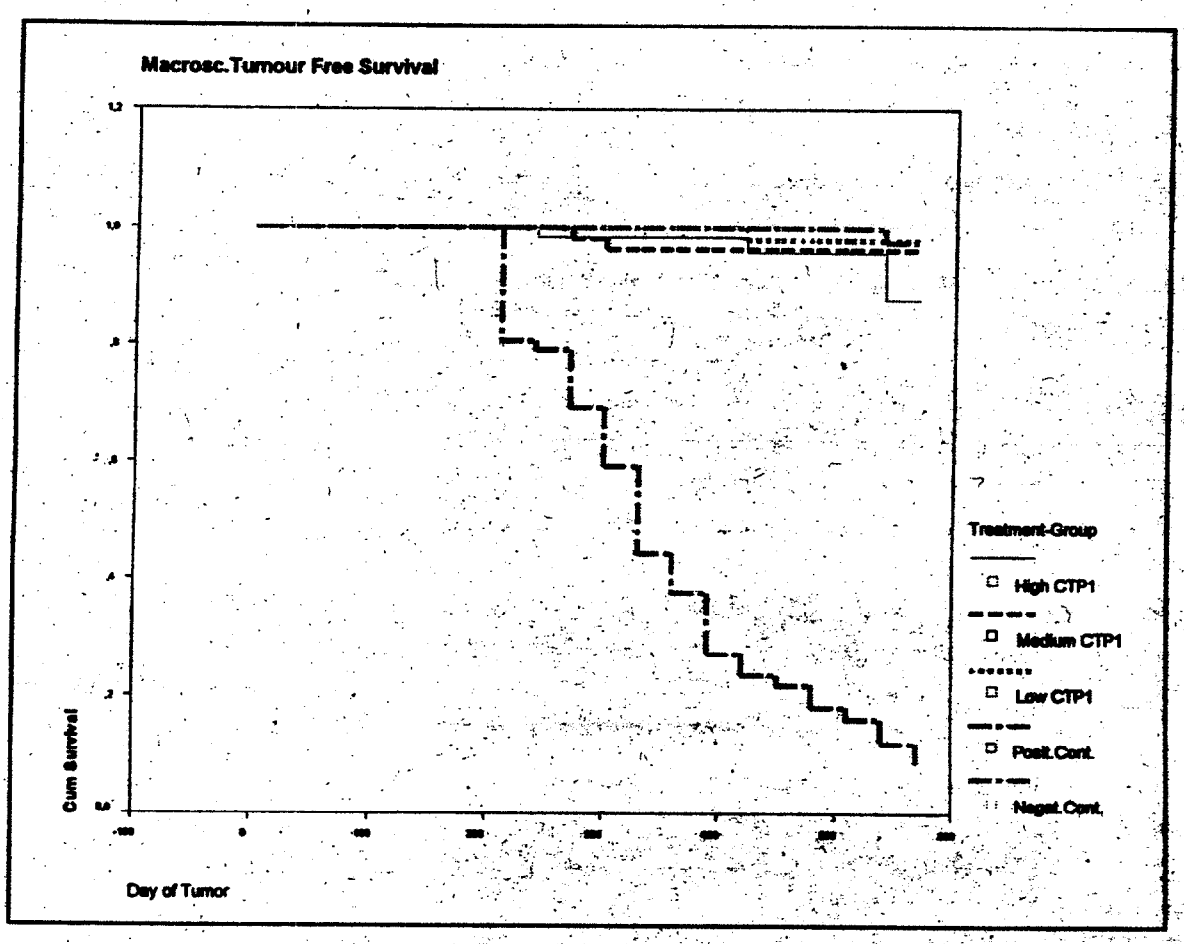
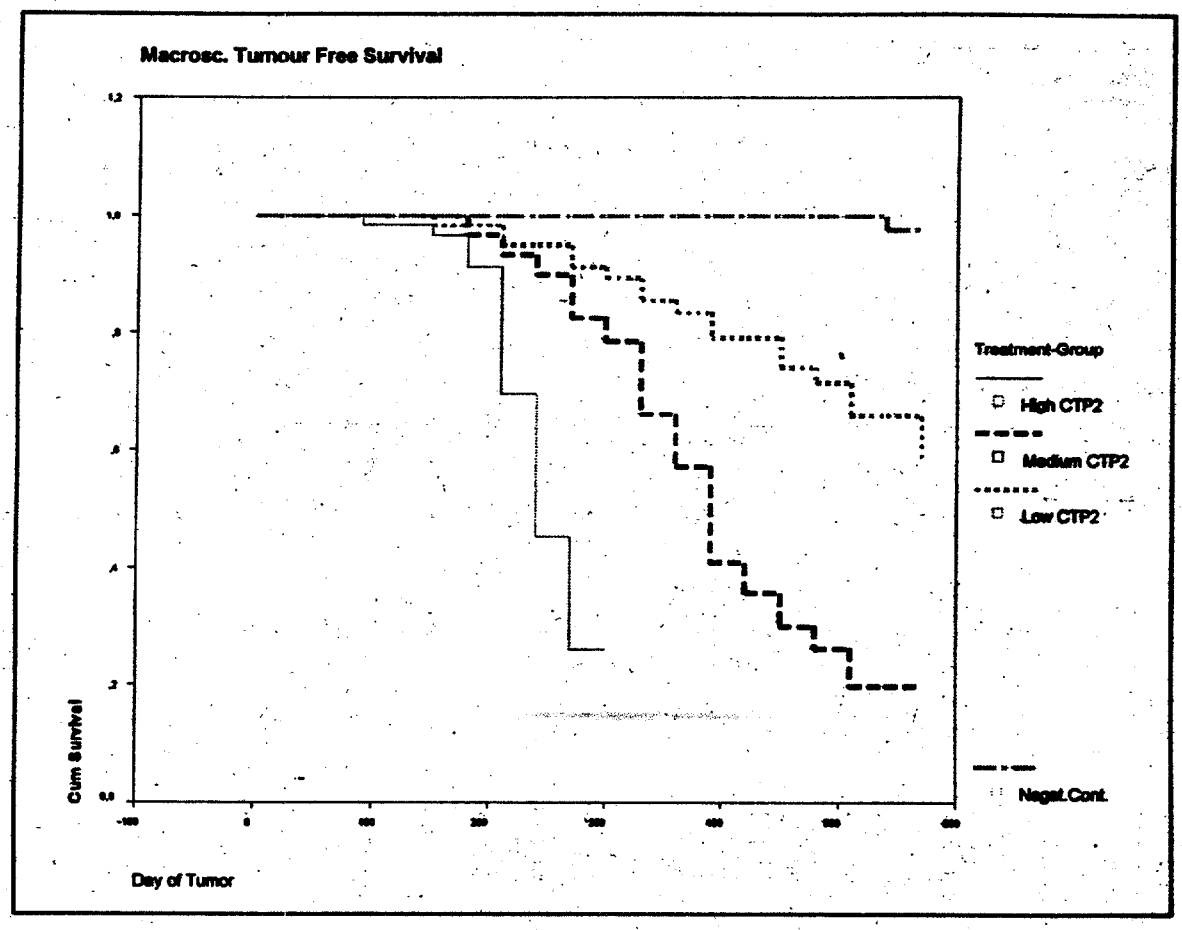


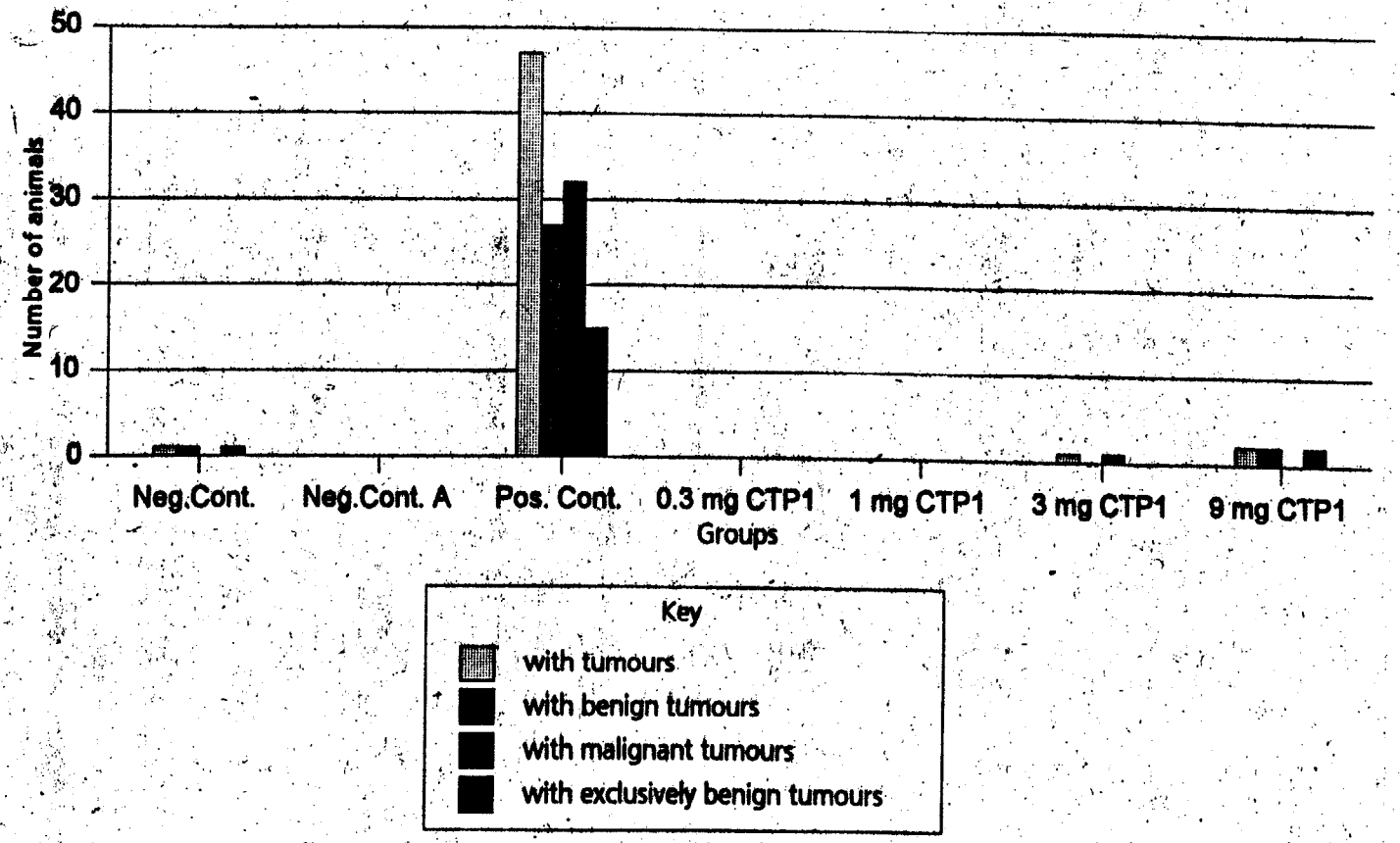
Figure 2 e:

Macroscopic Tumour Free Survival: CTP2



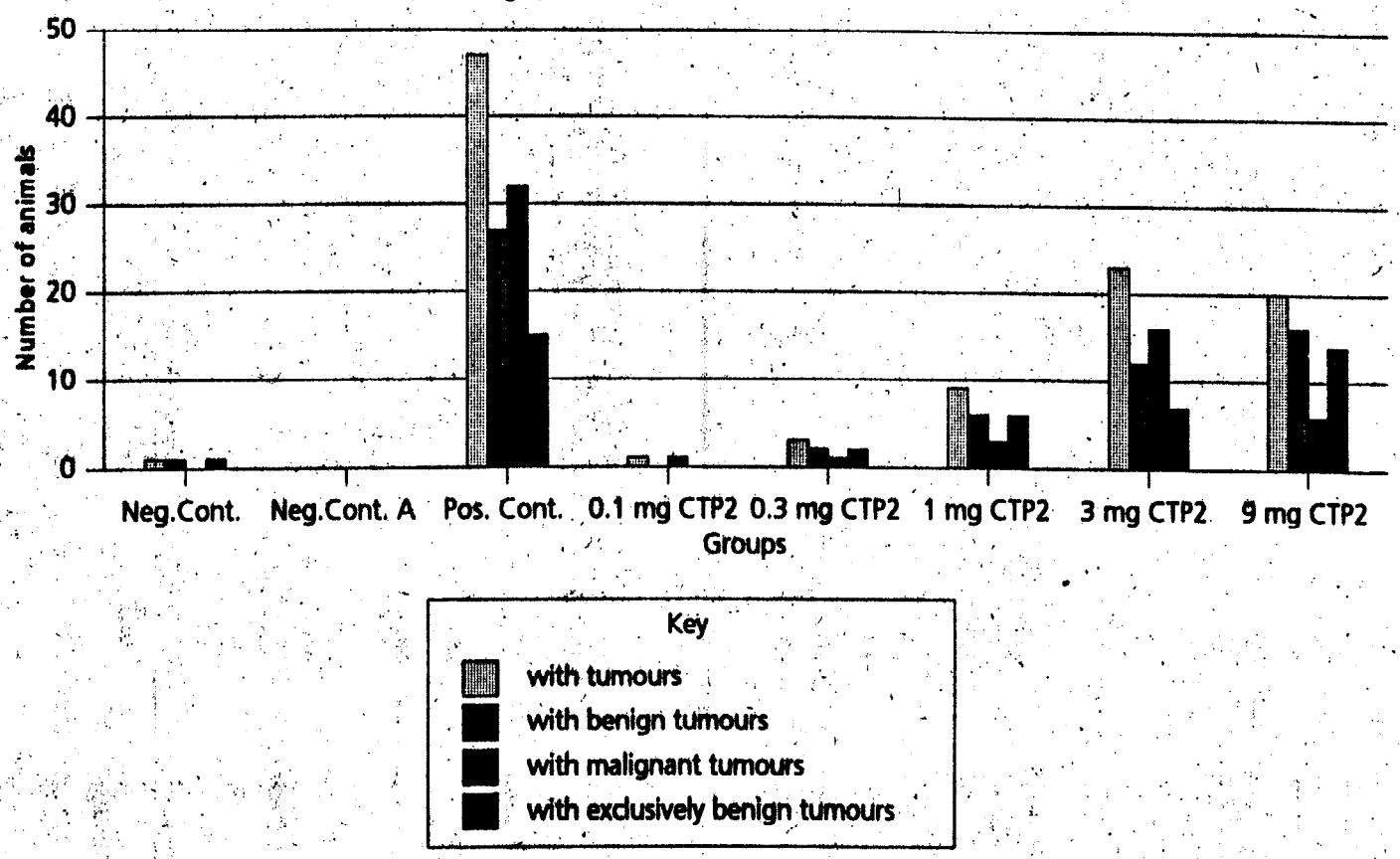
Dermal Carcinogenicity Study with CTP1

Fig. 3a: Tumours of the Skin



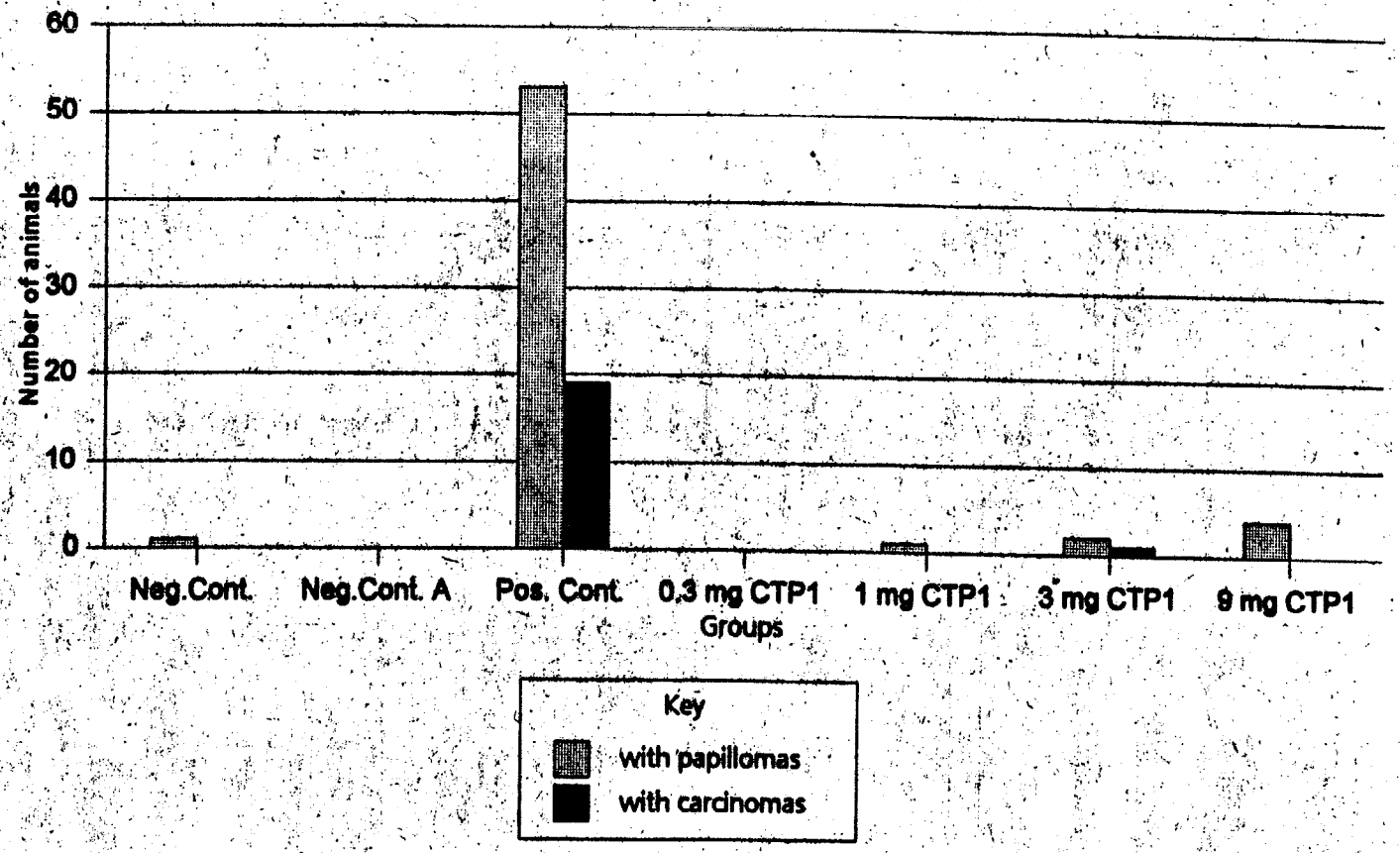
Dermal Carcinogenicity Study with CTP2

Fig. 3b: Tumours of the Skin



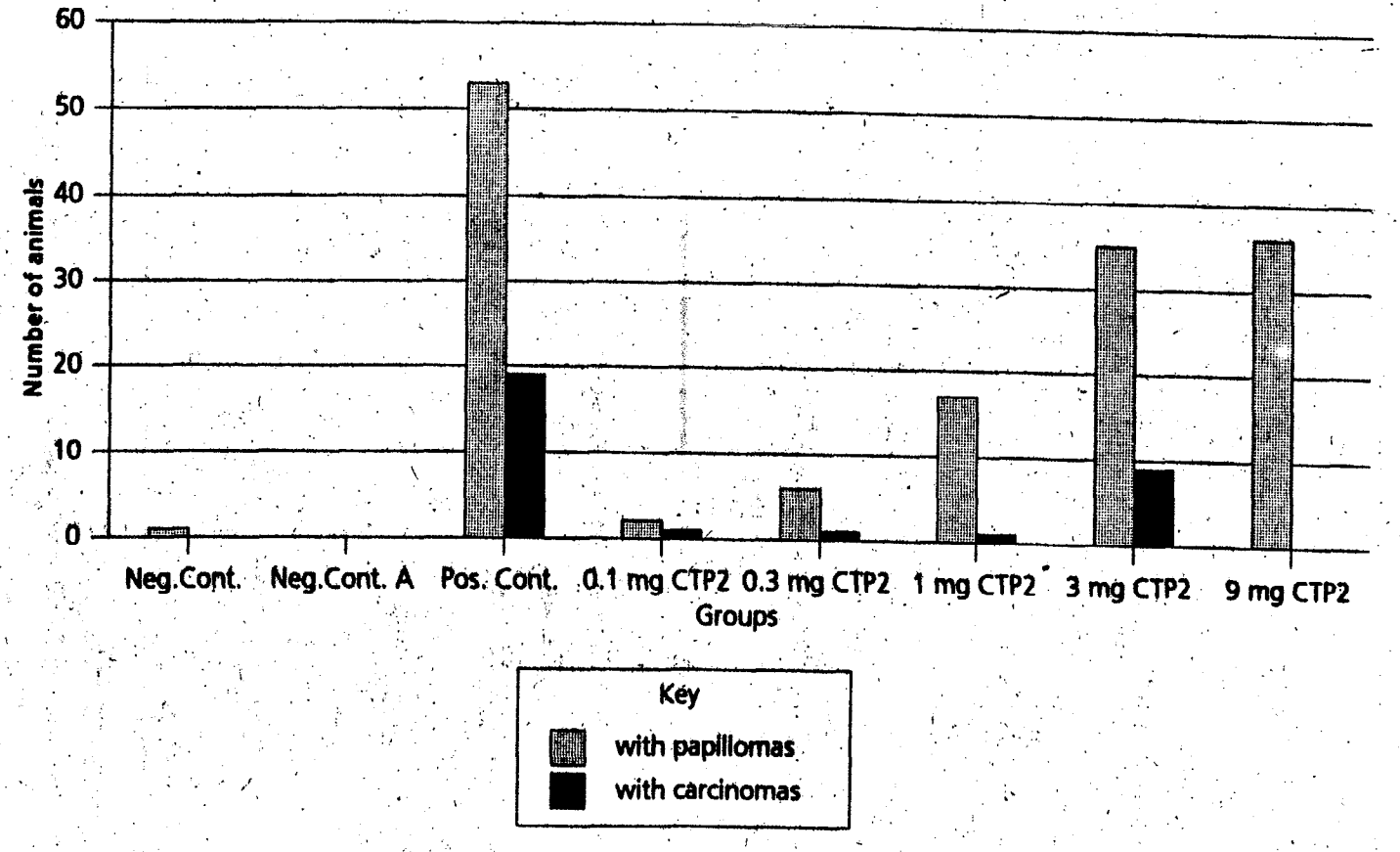
Dermal Carcinogenicity Study with CTP1

Fig. 4a: Macroscop. Tumours of the Skin



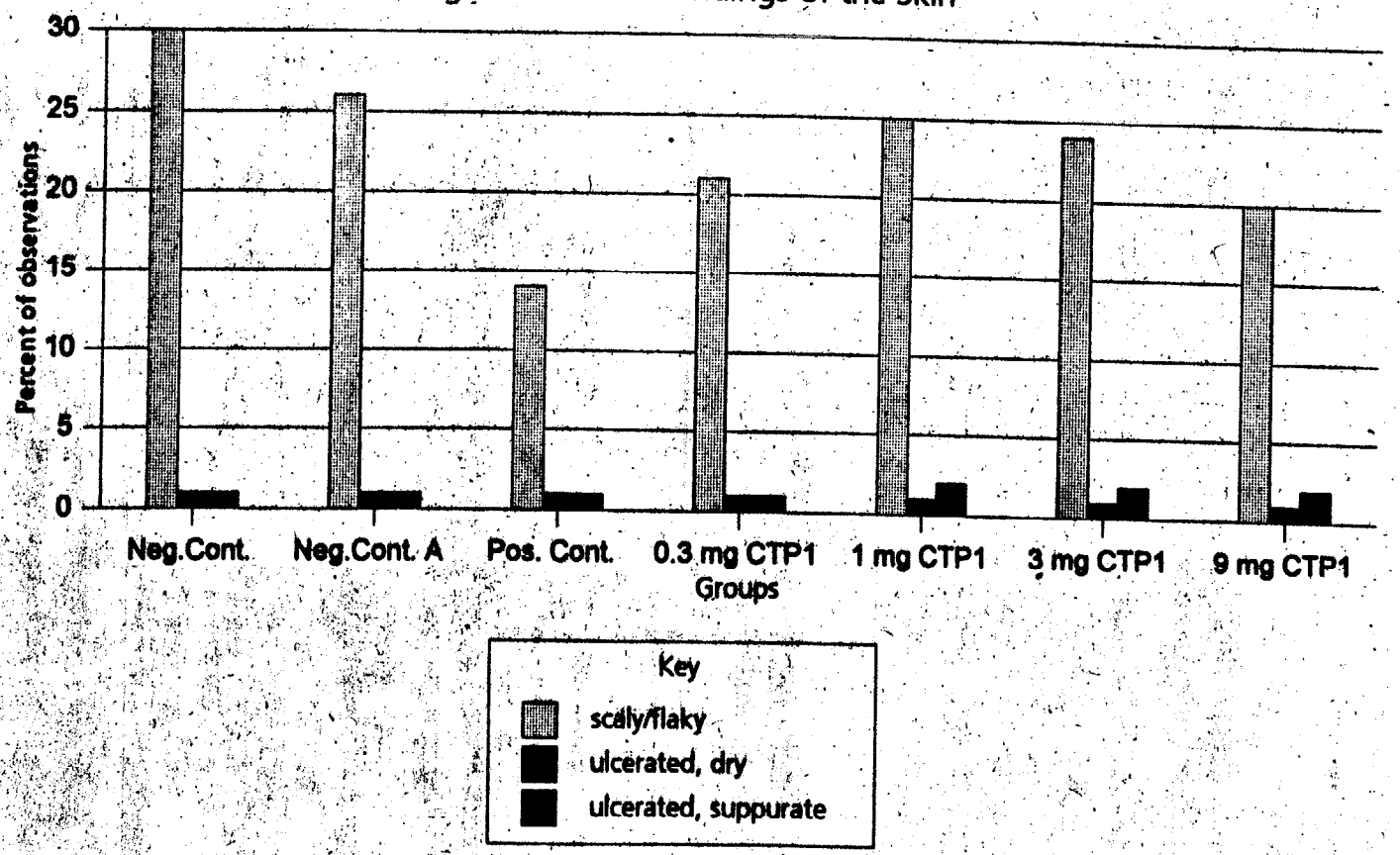
Dermal Carcinogenicity Study with CTP2

Fig. 4b: Macroscop. Tumours of the Skin



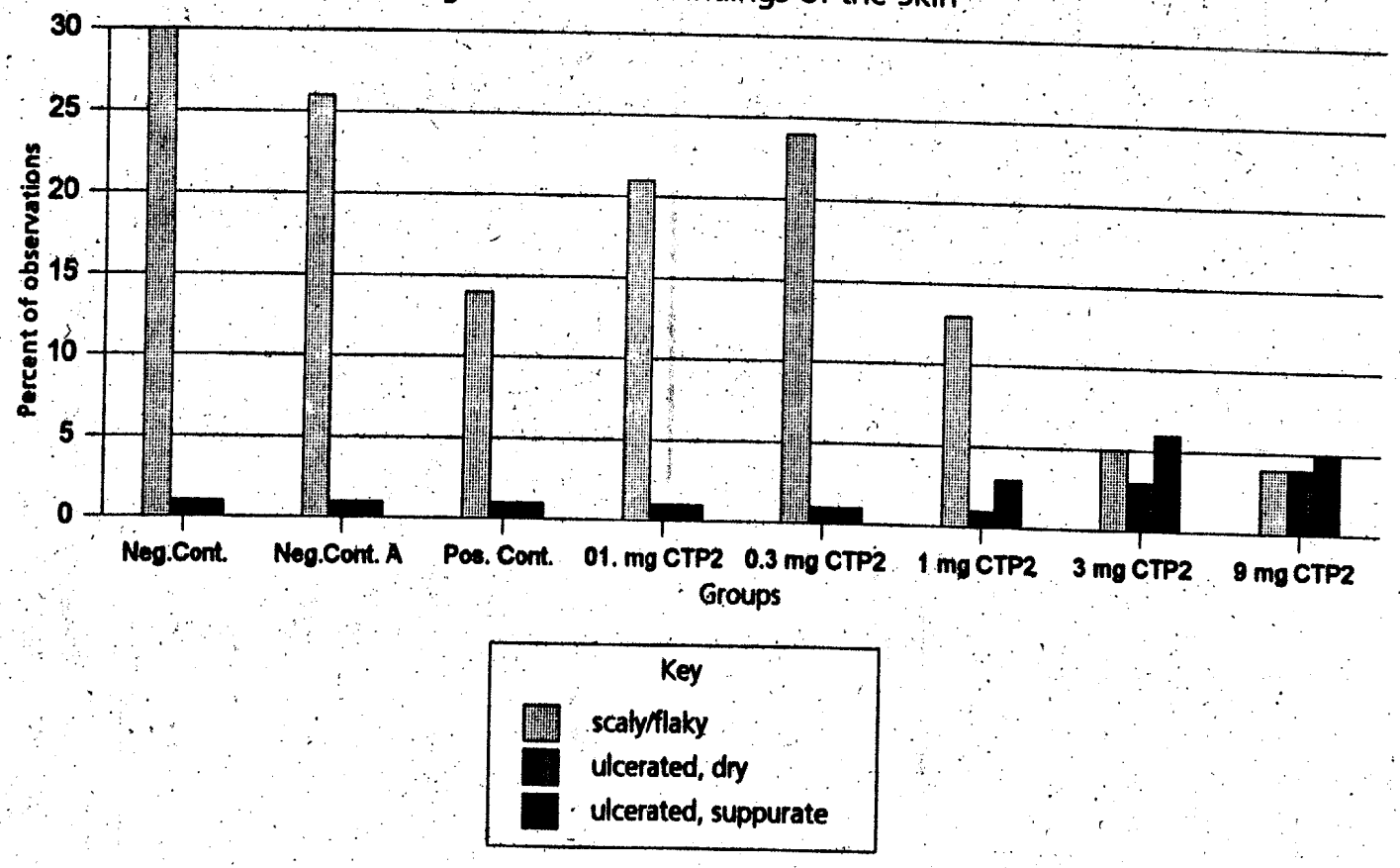
Dermal Carcinogenicity Study with CTP1

Fig. 5a: Selected Findings of the Skin



Dermal Carcinogenicity Study with CTP2

Fig. 5b: Selected Findings of the Skin



8. Appendix

In the appendix, the following abbreviations are generally used:

Negat. Cont.	Negative control group 01 (toluene, solvent control)
Posit. Cont.	Positive control group 02 (7.5 µg benzo(a)pyrene) per animal per application
Low CTP1	Low dose CTP1, group 03 (1 mg CTP1 per animal per application)
Medium CTP1	Medium dose CTP1, group 04 (3 mg CTP1 per animal per application)
High CTP1	High dose CTP1, group 05 (9 mg CTP1 per animal per application)
Low CTP2	Low dose CTP2, group 06 (1 mg CTP2 per animal per application)
Medium CTP2	Medium dose CTP2, group 07 (3 mg CTP2 per animal per application)
High CTP2	High dose CTP2, group 08 (9 mg CTP2 per animal per application)
Negat. Cont. A	Negative control group 09 of the additional groups (toluene)
Lower CTP1	Lower dose CTP1, group 10 (0.3 mg CTP1 per animal per application)
Lowest CTP2	Lowest dose CTP2, group 11 (0.1 mg CTP2 per animal per application)
Lower CTP2	Lower dose CTP2, group 12 (0.3 mg CTP2 per animal per application)
Anova	Analysis of variance

Appendix A: Individual Fate of the Animals

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

Individual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
Negat. Cont.	01	010001	Scheduled kill	546	29-May-95	
Negat. Cont.	01	010002	Scheduled kill	546	29-May-95	21
Negat. Cont.	01	010003	Scheduled kill	546	29-May-95	
Negat. Cont.	01	010004	Scheduled kill	547	30-May-95	
Negat. Cont.	01	010005	Found dead on study	439	11-Feb-95	
Negat. Cont.	01	010006	Scheduled kill	547	30-May-95	
Negat. Cont.	01	010007	Scheduled kill	547	30-May-95	
Negat. Cont.	01	010008	Unscheduled kill	11	10-Dec-93	
Negat. Cont.	01	010009	Unscheduled kill	472	16-Mar-95	33
Negat. Cont.	01	010010	Scheduled kill	547	30-May-95	3
Negat. Cont.	01	010011	Found dead on study	517	30-Apr-95	
Negat. Cont.	01	010012	Scheduled kill	547	30-May-95	
Negat. Cont.	01	010013	Scheduled kill	547	30-May-95	
Negat. Cont.	01	010014	Scheduled kill	547	30-May-95	
Negat. Cont.	01	010015	Found dead on study	401	04-Jan-95	
Negat. Cont.	01	010016	Found dead on study	484	28-Mar-95	
Negat. Cont.	01	010017	Scheduled kill	547	30-May-95	35
Negat. Cont.	01	010018	Unscheduled kill	291	16-Sep-94	
Negat. Cont.	01	010019	Scheduled kill	547	30-May-95	
Negat. Cont.	01	010020	Scheduled kill	548	31-May-95	
Negat. Cont.	01	010021	Scheduled kill	548	31-May-95	
Negat. Cont.	01	010022	Unscheduled kill	483	27-Mar-95	
Negat. Cont.	01	010023	Unscheduled kill	254	10-Aug-94	3
Negat. Cont.	01	010024	Unscheduled kill	543	26-May-95	
Negat. Cont.	01	010025	Scheduled kill	548	31-May-95	
Negat. Cont.	01	010026	Found dead on study	514	27-Apr-95	
Negat. Cont.	01	010027	Scheduled kill	548	31-May-95	2
Negat. Cont.	01	010028	Scheduled kill	548	31-May-95	
Negat. Cont.	01	010029	Unscheduled kill	479	23-Mar-95	
Negat. Cont.	01	010030	Found dead on study	532	15-May-95	
Negat. Cont.	01	010031	Unscheduled kill	364	28-Nov-94	
Negat. Cont.	01	010032	Unscheduled kill	512	25-Apr-95	
Negat. Cont.	01	010033	Scheduled kill	548	31-May-95	
Negat. Cont.	01	010034	Scheduled kill	548	31-May-95	
Negat. Cont.	01	010035	Found dead on study	515	28-Apr-95	
Negat. Cont.	01	010036	Scheduled kill	548	31-May-95	3
Negat. Cont.	01	010037	Unscheduled kill	435	07-Feb-95	
Negat. Cont.	01	010038	Found dead on study	204	21-Jun-94	
Negat. Cont.	01	010039	Scheduled kill	549	01-Jun-95	
Negat. Cont.	01	010040	Scheduled kill	549	01-Jun-95	
Negat. Cont.	01	010041	Scheduled kill	549	01-Jun-95	
Negat. Cont.	01	010042	Scheduled kill	549	01-Jun-95	
Negat. Cont.	01	010043	Scheduled kill	549	01-Jun-95	
Negat. Cont.	01	010044	Found dead on study	365	29-Nov-94	
Negat. Cont.	01	010045	Scheduled kill	549	01-Jun-95	
Negat. Cont.	01	010046	Unscheduled kill	492	05-Apr-95	
Negat. Cont.	01	010047	Unscheduled kill	466	10-Mar-95	
Negat. Cont.	01	010048	Scheduled kill	549	01-Jun-95	1
Negat. Cont.	01	010049	Found dead on study	545	28-May-95	
Negat. Cont.	01	010050	Scheduled kill	549	01-Jun-95	
Negat. Cont.	01	010051	Scheduled kill	549	01-Jun-95	
Negat. Cont.	01	010052	Found dead on study	45	13-Jan-94	
Negat. Cont.	01	010053	Scheduled kill	549	01-Jun-95	
Negat. Cont.	01	010054	Scheduled kill	549	01-Jun-95	
Negat. Cont.	01	010055	Scheduled kill	550	02-Jun-95	
Negat. Cont.	01	010056	Scheduled kill	550	02-Jun-95	
Negat. Cont.	01	010057	Scheduled kill	550	02-Jun-95	
Negat. Cont.	01	010058	Scheduled kill	550	02-Jun-95	
Negat. Cont.	01	010059	Unscheduled kill	515	28-Apr-95	5
Negat. Cont.	01	010060	Scheduled kill	550	02-Jun-95	
Negat. Cont.	01	010061	Found dead on study	503	16-Apr-95	17
Negat. Cont.	01	010062	Unscheduled kill	449	21-Feb-95	

Appendix A (continued): Individual Fate of the Animals

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

Individual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
Posit. Cont.	02	020001	Unscheduled kill	366	30-Nov-94	
Posit. Cont.	02	020002	Scheduled kill	546	29-May-95	
Posit. Cont.	02	020003	Scheduled kill	546	29-May-95	
Posit. Cont.	02	020004	Unscheduled kill	448	20-Feb-95	1
Posit. Cont.	02	020005	Unscheduled kill	527	10-May-95	8
Posit. Cont.	02	020006	Found dead on study	389	23-Dec-94	
Posit. Cont.	02	020007	Unscheduled kill	444	16-Feb-95	
Posit. Cont.	02	020008	Unscheduled kill	303	28-Sep-94	5
Posit. Cont.	02	020009	Scheduled kill	546	29-May-95	16
Posit. Cont.	02	020010	Unscheduled kill	463	07-Mar-95	1
Posit. Cont.	02	020011	Unscheduled kill	438	10-Feb-95	
Posit. Cont.	02	020012	Scheduled kill	547	30-May-95	
Posit. Cont.	02	020013	Unscheduled kill	487	31-Mar-95	4
Posit. Cont.	02	020014	Unscheduled kill	261	17-Aug-94	
Posit. Cont.	02	020015	Found dead on study	454	26-Feb-95	
Posit. Cont.	02	020016	Scheduled kill	547	30-May-95	
Posit. Cont.	02	020017	Scheduled kill	547	30-May-95	14
Posit. Cont.	02	020018	Scheduled kill	547	30-May-95	
Posit. Cont.	02	020019	Scheduled kill	547	30-May-95	1
Posit. Cont.	02	020020	Found dead on study	448	20-Feb-95	11
Posit. Cont.	02	020021	Unscheduled kill	421	24-Jan-95	7
Posit. Cont.	02	020022	Scheduled kill	547	30-May-95	
Posit. Cont.	02	020023	Scheduled kill	548	31-May-95	
Posit. Cont.	02	020024	Scheduled kill	548	31-May-95	
Posit. Cont.	02	020025	Unscheduled kill	452	24-Feb-95	
Posit. Cont.	02	020026	Scheduled kill	548	31-May-95	
Posit. Cont.	02	020027	Unscheduled kill	345	09-Nov-94	13
Posit. Cont.	02	020028	Unscheduled kill	351	15-Nov-94	1
Posit. Cont.	02	020029	Scheduled kill	548	31-May-95	8
Posit. Cont.	02	020030	Scheduled kill	548	31-May-95	8
Posit. Cont.	02	020031	Unscheduled kill	455	27-Feb-95	10
Posit. Cont.	02	020032	Scheduled kill	548	31-May-95	
Posit. Cont.	02	020033	Scheduled kill	549	01-Jun-95	1
Posit. Cont.	02	020034	Unscheduled kill	465	09-Mar-95	4
Posit. Cont.	02	020035	Found dead on study	414	17-Jan-95	
Posit. Cont.	02	020036	Scheduled kill	549	01-Jun-95	1
Posit. Cont.	02	020037	Scheduled kill	549	01-Jun-95	1
Posit. Cont.	02	020038	Found dead on study	514	27-Apr-95	14
Posit. Cont.	02	020039	Unscheduled kill	511	24-Apr-95	1
Posit. Cont.	02	020040	Scheduled kill	549	01-Jun-95	4
Posit. Cont.	02	020041	Unscheduled kill	511	24-Apr-95	1
Posit. Cont.	02	020042	Scheduled kill	549	01-Jun-95	
Posit. Cont.	02	020043	Unscheduled kill	525	08-May-95	
Posit. Cont.	02	020044	Scheduled kill	549	01-Jun-95	
Posit. Cont.	02	020045	Unscheduled kill	437	09-Feb-95	7
Posit. Cont.	02	020046	Unscheduled kill	491	04-Apr-95	2
Posit. Cont.	02	020047	Scheduled kill	550	02-Jun-95	
Posit. Cont.	02	020048	Scheduled kill	550	02-Jun-95	
Posit. Cont.	02	020049	Found dead on study	429	01-Feb-95	
Posit. Cont.	02	020050	Found dead on study	309	04-Oct-94	8
Posit. Cont.	02	020051	Unscheduled kill	471	15-Mar-95	
Posit. Cont.	02	020052	Unscheduled kill	505	18-Apr-95	
Posit. Cont.	02	020053	Found dead on study	356	20-Nov-94	
Posit. Cont.	02	020054	Unscheduled kill	378	12-Dec-94	1
Posit. Cont.	02	020055	Unscheduled kill	415	18-Jan-95	
Posit. Cont.	02	020056	Unscheduled kill	395	29-Dec-94	
Posit. Cont.	02	020057	Unscheduled kill	519	02-May-95	
Posit. Cont.	02	020058	Scheduled kill	550	02-Jun-95	3
Posit. Cont.	02	020059	Unscheduled kill	322	17-Oct-94	7
Posit. Cont.	02	020060	Unscheduled kill	483	27-Mar-95	1
Posit. Cont.	02	020061	Found dead on study	380	14-Dec-94	
Posit. Cont.	02	020062	Scheduled kill	550	02-Jun-95	4

Appendix A (continued): Individual Fate of the Animals

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

Individual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
Low CTP1	03	030001	Found dead on study	416	19-Jan-95	
Low CTP1	03	030002	Unscheduled kill	534	17-May-95	6
Low CTP1	03	030003	Unscheduled kill	345	09-Nov-94	
Low CTP1	03	030004	Unscheduled kill	416	19-Jan-95	1
Low CTP1	03	030005	Unscheduled kill	415	18-Jan-95	
Low CTP1	03	030006	Scheduled kill	546	29-May-95	
Low CTP1	03	030007	Unscheduled kill	442	14-Feb-95	
Low CTP1	03	030008	Scheduled kill	546	29-May-95	
Low CTP1	03	030009	Found dead on study	414	17-Jan-95	14
Low CTP1	03	030010	Scheduled kill	546	29-May-95	
Low CTP1	03	030011	Scheduled kill	547	30-May-95	
Low CTP1	03	030012	Scheduled kill	547	30-May-95	
Low CTP1	03	030013	Unscheduled kill	438	10-Feb-95	
Low CTP1	03	030014	Scheduled kill	547	30-May-95	
Low CTP1	03	030015	Scheduled kill	547	30-May-95	
Low CTP1	03	030016	Scheduled kill	547	30-May-95	
Low CTP1	03	030017	Unscheduled kill	491	04-Apr-95	
Low CTP1	03	030018	Scheduled kill	547	30-May-95	
Low CTP1	03	030019	Scheduled kill	548	31-May-95	
Low CTP1	03	030020	Found dead on study	461	05-Mar-95	16
Low CTP1	03	030021	Found dead on study	440	12-Feb-95	
Low CTP1	03	030022	Scheduled kill	548	31-May-95	
Low CTP1	03	030023	Scheduled kill	548	31-May-95	
Low CTP1	03	030024	Unscheduled kill	470	14-Mar-95	
Low CTP1	03	030025	Unscheduled kill	317	12-Oct-94	8
Low CTP1	03	030026	Unscheduled kill	484	28-Mar-95	
Low CTP1	03	030027	Scheduled kill	548	31-May-95	
Low CTP1	03	030028	Scheduled kill	548	31-May-95	26
Low CTP1	03	030029	Scheduled kill	548	31-May-95	
Low CTP1	03	030030	Unscheduled kill	528	11-May-95	1
Low CTP1	03	030031	Scheduled kill	548	31-May-95	
Low CTP1	03	030032	Scheduled kill	549	01-Jun-95	
Low CTP1	03	030033	Unscheduled kill	319	14-Oct-94	24
Low CTP1	03	030034	Unscheduled kill	441	13-Feb-95	15
Low CTP1	03	030035	Unscheduled kill	471	15-Mar-95	
Low CTP1	03	030036	Scheduled kill	549	01-Jun-95	21
Low CTP1	03	030037	Unscheduled kill	535	18-May-95	20
Low CTP1	03	030038	Scheduled kill	549	01-Jun-95	
Low CTP1	03	030039	Found dead on study	248	04-Aug-94	
Low CTP1	03	030040	Found dead on study	496	09-Apr-95	
Low CTP1	03	030041	Scheduled kill	549	01-Jun-95	5
Low CTP1	03	030042	Scheduled kill	549	01-Jun-95	
Low CTP1	03	030043	Scheduled kill	549	01-Jun-95	
Low CTP1	03	030044	Scheduled kill	549	01-Jun-95	
Low CTP1	03	030045	Unscheduled kill	381	15-Dec-94	12
Low CTP1	03	030046	Unscheduled kill	373	07-Dec-94	13
Low CTP1	03	030047	Unscheduled kill	414	17-Jan-95	14
Low CTP1	03	030048	Scheduled kill	549	01-Jun-95	
Low CTP1	03	030049	Found dead on study	398	01-Jan-95	
Low CTP1	03	030050	Unscheduled kill	312	07-Oct-94	11
Low CTP1	03	030051	Unscheduled kill	528	11-May-95	
Low CTP1	03	030052	Scheduled kill	550	02-Jun-95	
Low CTP1	03	030053	Unscheduled kill	339	03-Nov-94	18
Low CTP1	03	030054	Scheduled kill	550	02-Jun-95	
Low CTP1	03	030055	Unscheduled kill	505	18-Apr-95	
Low CTP1	03	030056	Unscheduled kill	409	12-Jan-95	
Low CTP1	03	030057	Unscheduled kill	414	17-Jan-95	1
Low CTP1	03	030058	Scheduled kill	550	02-Jun-95	
Low CTP1	03	030059	Scheduled kill	550	02-Jun-95	
Low CTP1	03	030060	Found dead on study	497	10-Apr-95	
Low CTP1	03	030061	Unscheduled kill	424	27-Jan-95	
Low CTP1	03	030062	Unscheduled kill	452	24-Feb-95	22

Appendix A (continued): Individual Fate of the Animals

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

Individual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
Medium CTP1	04	040001	Scheduled kill	546	29-May-95	
Medium CTP1	04	040002	Scheduled kill	546	29-May-95	
Medium CTP1	04	040003	Found dead on study	490	03-Apr-95	
Medium CTP1	04	040004	Scheduled kill	546	29-May-95	
Medium CTP1	04	040005	Scheduled kill	547	30-May-95	
Medium CTP1	04	040006	Unscheduled kill	420	23-Jan-95	9
Medium CTP1	04	040007	Unscheduled kill	512	25-Apr-95	1
Medium CTP1	04	040008	Unscheduled kill	340	04-Nov-94	10
Medium CTP1	04	040009	Unscheduled kill	469	13-Mar-95	13
Medium CTP1	04	040010	Found dead on study	453	25-Feb-95	
Medium CTP1	04	040011	Scheduled kill	547	30-May-95	7
Medium CTP1	04	040012	Scheduled kill	547	30-May-95	
Medium CTP1	04	040013	Scheduled kill	547	30-May-95	
Medium CTP1	04	040014	Unscheduled kill	457	01-Mar-95	
Medium CTP1	04	040015	Scheduled kill	547	30-May-95	
Medium CTP1	04	040016	Unscheduled kill	400	03-Jan-95	
Medium CTP1	04	040017	Found dead on study	228	15-Jul-94	3
Medium CTP1	04	040018	Scheduled kill	547	30-May-95	
Medium CTP1	04	040019	Scheduled kill	548	31-May-95	
Medium CTP1	04	040020	Unscheduled kill	396	30-Dec-94	18
Medium CTP1	04	040021	Unscheduled kill	535	18-May-95	10
Medium CTP1	04	040022	Found dead on study	497	10-Apr-95	
Medium CTP1	04	040023	Unscheduled kill	421	24-Jan-95	34
Medium CTP1	04	040024	Scheduled kill	548	31-May-95	
Medium CTP1	04	040025	Unscheduled kill	519	02-May-95	
Medium CTP1	04	040026	Scheduled kill	548	31-May-95	
Medium CTP1	04	040027	Unscheduled kill	487	31-Mar-95	
Medium CTP1	04	040028	Unscheduled kill	406	09-Jan-95	19
Medium CTP1	04	040029	Scheduled kill	548	31-May-95	1
Medium CTP1	04	040030	Scheduled kill	548	31-May-95	
Medium CTP1	04	040031	Unscheduled kill	545	28-May-95	
Medium CTP1	04	040032	Found dead on study	225	12-Jul-94	
Medium CTP1	04	040033	Scheduled kill	548	31-May-95	
Medium CTP1	04	040034	Scheduled kill	549	01-Jun-95	
Medium CTP1	04	040035	Scheduled kill	549	01-Jun-95	13
Medium CTP1	04	040036	Unscheduled kill	269	25-Aug-94	7
Medium CTP1	04	040037	Unscheduled kill	317	12-Oct-94	15
Medium CTP1	04	040038	Scheduled kill	549	01-Jun-95	
Medium CTP1	04	040039	Unscheduled kill	395	29-Dec-94	
Medium CTP1	04	040040	Unscheduled kill	172	20-May-94	
Medium CTP1	04	040041	Found dead on study	500	13-Apr-95	
Medium CTP1	04	040042	Scheduled kill	549	01-Jun-95	
Medium CTP1	04	040043	Unscheduled kill	422	25-Jan-95	
Medium CTP1	04	040044	Unscheduled kill	232	19-Jul-94	
Medium CTP1	04	040045	Scheduled kill	549	01-Jun-95	38
Medium CTP1	04	040046	Unscheduled kill	506	19-Apr-95	1
Medium CTP1	04	040047	Unscheduled kill	346	10-Nov-94	19
Medium CTP1	04	040048	Found dead on study	541	26-May-95	
Medium CTP1	04	040049	Found dead on study	473	17-Mar-95	
Medium CTP1	04	040050	Unscheduled kill	395	29-Dec-94	16
Medium CTP1	04	040051	Scheduled kill	549	01-Jun-95	
Medium CTP1	04	040052	Found dead on study	538	21-May-95	3
Medium CTP1	04	040053	Scheduled kill	549	01-Jun-95	
Medium CTP1	04	040054	Found dead on study	538	21-May-95	
Medium CTP1	04	040055	Scheduled kill	550	02-Jun-95	
Medium CTP1	04	040056	Scheduled kill	550	02-Jun-95	
Medium CTP1	04	040057	Unscheduled kill	520	03-May-95	1
Medium CTP1	04	040058	Unscheduled kill	201	17-Aug-94	11
Medium CTP1	04	040059	Unscheduled kill	463	07-Mar-95	13
Medium CTP1	04	040060	Unscheduled kill	234	21-Jul-94	3
Medium CTP1	04	040061	Scheduled kill	550	02-Jun-95	
Medium CTP1	04	040062	Scheduled kill	550	02-Jun-95	

Appendix A (continued): Individual Fate of the Animals

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

Individual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
High CTP1	05	050001	Unscheduled kill	490	03-Apr-95	
High CTP1	05	050002	Unscheduled kill	416	19-Jan-95	1
High CTP1	05	050003	Unscheduled kill	241	28-Jul-94	
High CTP1	05	050004	Unscheduled kill	417	20-Jan-95	
High CTP1	05	050005	Scheduled kill	546	29-May-95	
High CTP1	05	050006	Unscheduled kill	219	06-Jul-94	
High CTP1	05	050007	Found dead on study	384	18-Dec-94	
High CTP1	05	050008	Scheduled kill	546	29-May-95	
High CTP1	05	050009	Unscheduled kill	388	22-Dec-94	26
High CTP1	05	050010	Unscheduled kill	494	07-Apr-95	
High CTP1	05	050011	Unscheduled kill	346	10-Nov-94	17
High CTP1	05	050012	Unscheduled kill	347	11-Nov-94	19
High CTP1	05	050013	Unscheduled kill	421	24-Jan-95	13
High CTP1	05	050014	Found dead on study	467	11-Mar-95	
High CTP1	05	050015	Scheduled kill	546	29-May-95	
High CTP1	05	050016	Scheduled kill	547	30-May-95	
High CTP1	05	050017	Scheduled kill	547	30-May-95	8
High CTP1	05	050018	Scheduled kill	547	30-May-95	
High CTP1	05	050019	Found dead on study	546	29-May-95	
High CTP1	05	050020	Unscheduled kill	536	19-May-95	
High CTP1	05	050021	Scheduled kill	547	30-May-95	
High CTP1	05	050022	Unscheduled kill	256	12-Aug-94	5
High CTP1	05	050023	Unscheduled kill	469	13-Mar-95	
High CTP1	05	050024	Unscheduled kill	452	24-Feb-95	
High CTP1	05	050025	Scheduled kill	547	30-May-95	
High CTP1	05	050026	Found dead on study	385	19-Dec-94	
High CTP1	05	050027	Found dead on study	448	20-Feb-95	
High CTP1	05	050028	Scheduled kill	547	30-May-95	
High CTP1	05	050029	Unscheduled kill	312	07-Oct-94	10
High CTP1	05	050030	Scheduled kill	548	31-May-95	
High CTP1	05	050031	Unscheduled kill	247	03-Aug-94	10
High CTP1	05	050032	Unscheduled kill	450	22-Feb-95	
High CTP1	05	050033	Unscheduled kill	261	17-Aug-94	10
High CTP1	05	050034	Scheduled kill	548	31-May-95	1
High CTP1	05	050035	Found dead on study	481	25-Mar-95	
High CTP1	05	050036	Unscheduled kill	415	18-Jan-95	
High CTP1	05	050037	Found dead on study	389	23-Dec-94	
High CTP1	05	050038	Unscheduled kill	396	30-Dec-94	15
High CTP1	05	050039	Unscheduled kill	543	26-May-95	
High CTP1	05	050040	Unscheduled kill	214	01-Jul-94	1
High CTP1	05	050041	Unscheduled kill	464	08-Mar-95	
High CTP1	05	050042	Unscheduled kill	529	12-May-95	
High CTP1	05	050043	Found dead on study	344	08-Nov-94	
High CTP1	05	050044	Unscheduled kill	340	04-Nov-94	18
High CTP1	05	050045	Scheduled kill	548	31-May-95	
High CTP1	05	050046	Unscheduled kill	539	22-May-95	39
High CTP1	05	050047	Scheduled kill	548	31-May-95	3
High CTP1	05	050048	Scheduled kill	548	31-May-95	22
High CTP1	05	050049	Found dead on study	484	28-Mar-95	
High CTP1	05	050050	Scheduled kill	549	01-Jun-95	
High CTP1	05	050051	Scheduled kill	549	01-Jun-95	
High CTP1	05	050052	Unscheduled kill	498	11-Apr-95	
High CTP1	05	050053	Scheduled kill	549	01-Jun-95	
High CTP1	05	050054	Unscheduled kill	402	05-Jan-95	18
High CTP1	05	050055	Unscheduled kill	525	08-May-95	1
High CTP1	05	050056	Unscheduled kill	256	12-Aug-94	12
High CTP1	05	050057	Scheduled kill	549	01-Jun-95	
High CTP1	05	050058	Scheduled kill	550	02-Jun-95	24
High CTP1	05	050059	Unscheduled kill	368	02-Dec-94	41
High CTP1	05	050060	Unscheduled kill	305	30-Sep-94	17
High CTP1	05	050061	Found dead on study	230	17-Jul-94	5
High CTP1	05	050062	Scheduled kill	550	02-Jun-95	3

Appendix A (continued): Individual Fate of the Animals

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

Individual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
Low CTP2	06	060001	Scheduled kill	546	29-May-95	
Low CTP2	06	060002	Found dead on study	412	15-Jan-95	1
Low CTP2	06	060003	Unscheduled kill	336	31-Oct-94	3
Low CTP2	06	060004	Found dead on study	59	27-Jan-94	
Low CTP2	06	060005	Found dead on study	247	03-Aug-94	2
Low CTP2	06	060006	Scheduled kill	546	29-May-95	
Low CTP2	06	060007	Scheduled kill	546	29-May-95	
Low CTP2	06	060008	Scheduled kill	547	30-May-95	
Low CTP2	06	060009	Scheduled kill	547	30-May-95	1
Low CTP2	06	060010	Found dead on study	482	26-Mar-95	26
Low CTP2	06	060011	Scheduled kill	547	30-May-95	
Low CTP2	06	060012	Unscheduled kill	417	20-Jan-95	
Low CTP2	06	060013	Unscheduled kill	428	31-Jan-95	
Low CTP2	06	060014	Found dead on study	511	24-Apr-95	2
Low CTP2	06	060015	Found dead on study	297	22-Sep-94	
Low CTP2	06	060016	Scheduled kill	547	30-May-95	
Low CTP2	06	060017	Scheduled kill	547	30-May-95	
Low CTP2	06	060018	Unscheduled kill	255	11-Aug-94	13
Low CTP2	06	060019	Scheduled kill	547	30-May-95	
Low CTP2	06	060020	Unscheduled kill	39	07-Jan-94	
Low CTP2	06	060021	Found dead on study	366	30-Nov-94	15
Low CTP2	06	060022	Scheduled kill	548	31-May-95	
Low CTP2	06	060023	Unscheduled kill	210	27-Jun-94	
Low CTP2	06	060024	Found dead on study	548	31-May-95	17
Low CTP2	06	060025	Unscheduled kill	255	11-Aug-94	13
Low CTP2	06	060026	Scheduled kill	548	31-May-95	
Low CTP2	06	060027	Unscheduled kill	543	26-May-95	30
Low CTP2	06	060028	Scheduled kill	548	31-May-95	
Low CTP2	06	060029	Found dead on study	379	13-Dec-94	27
Low CTP2	06	060030	Unscheduled kill	371	05-Dec-94	16
Low CTP2	06	060031	Scheduled kill	548	31-May-95	
Low CTP2	06	060032	Unscheduled kill	229	16-Jul-94	5
Low CTP2	06	060033	Unscheduled kill	514	27-Apr-95	
Low CTP2	06	060034	Found dead on study	502	15-Apr-95	
Low CTP2	06	060035	Unscheduled kill	522	05-May-95	
Low CTP2	06	060036	Unscheduled kill	445	17-Feb-95	7
Low CTP2	06	060037	Scheduled kill	548	31-May-95	
Low CTP2	06	060038	Scheduled kill	548	31-May-95	15
Low CTP2	06	060039	Scheduled kill	549	01-Jun-95	5
Low CTP2	06	060040	Scheduled kill	549	01-Jun-95	
Low CTP2	06	060041	Unscheduled kill	358	22-Nov-94	
Low CTP2	06	060042	Scheduled kill	549	01-Jun-95	
Low CTP2	06	060043	Unscheduled kill	536	19-May-95	
Low CTP2	06	060044	Unscheduled kill	389	23-Dec-94	18
Low CTP2	06	060045	Scheduled kill	549	01-Jun-95	
Low CTP2	06	060046	Scheduled kill	550	02-Jun-95	
Low CTP2	06	060047	Unscheduled kill	475	19-Mar-95	
Low CTP2	06	060048	Found dead on study	468	12-Mar-95	
Low CTP2	06	060049	Unscheduled kill	388	22-Dec-94	32
Low CTP2	06	060050	Scheduled kill	550	02-Jun-95	
Low CTP2	06	060051	Unscheduled kill	387	21-Dec-94	48
Low CTP2	06	060052	Unscheduled kill	537	20-May-95	
Low CTP2	06	060053	Unscheduled kill	406	09-Jan-95	7
Low CTP2	06	060054	Unscheduled kill	511	24-Apr-95	1
Low CTP2	06	060055	Scheduled kill	550	02-Jun-95	
Low CTP2	06	060056	Scheduled kill	550	02-Jun-95	
Low CTP2	06	060057	Unscheduled kill	490	03-Apr-95	1
Low CTP2	06	060058	Found dead on study	16	15-Dec-93	
Low CTP2	06	060059	Unscheduled kill	247	03-Aug-94	
Low CTP2	06	060060	Found dead on study	487	31-Mar-95	
Low CTP2	06	060061	Unscheduled kill	393	27-Dec-94	7
Low CTP2	06	060062	Unscheduled kill	368	02-Dec-94	1

Appendix A (continued): Individual Fate of the Animals

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

Individual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
Medium CTP2	07	070001	Unscheduled kill	261	17-Aug-94	11
Medium CTP2	07	070002	Scheduled kill	547	30-May-95	3
Medium CTP2	07	070003	Unscheduled kill	420	23-Jan-95	6
Medium CTP2	07	070004	Found dead on study	355	19-Nov-94	24
Medium CTP2	07	070005	Scheduled kill	547	30-May-95	
Medium CTP2	07	070006	Scheduled kill	547	30-May-95	3
Medium CTP2	07	070007	Found dead on study	299	24-Sep-94	6
Medium CTP2	07	070008	Unscheduled kill	157	05-May-94	
Medium CTP2	07	070009	Unscheduled kill	541	24-May-95	32
Medium CTP2	07	070010	Found dead on study	456	28-Feb-95	12
Medium CTP2	07	070011	Unscheduled kill	436	08-Feb-95	8
Medium CTP2	07	070012	Unscheduled kill	443	15-Feb-95	12
Medium CTP2	07	070013	Unscheduled kill	347	11-Nov-94	16
Medium CTP2	07	070014	Scheduled kill	548	31-May-95	12
Medium CTP2	07	070015	Unscheduled kill	424	27-Jan-95	24
Medium CTP2	07	070016	Unscheduled kill	305	30-Sep-94	9
Medium CTP2	07	070017	Unscheduled kill	413	16-Jan-95	47
Medium CTP2	07	070018	Scheduled kill	548	31-May-95	
Medium CTP2	07	070019	Unscheduled kill	380	14-Dec-94	15
Medium CTP2	07	070020	Unscheduled kill	533	16-May-95	12
Medium CTP2	07	070021	Scheduled kill	548	31-May-95	39
Medium CTP2	07	070022	Unscheduled kill	421	24-Jan-95	18
Medium CTP2	07	070023	Scheduled kill	549	01-Jun-95	5
Medium CTP2	07	070024	Scheduled kill	549	01-Jun-95	
Medium CTP2	07	070025	Unscheduled kill	521	04-May-95	6
Medium CTP2	07	070026	Unscheduled kill	417	20-Jan-95	22
Medium CTP2	07	070027	Unscheduled kill	396	30-Dec-94	
Medium CTP2	07	070028	Unscheduled kill	382	16-Dec-94	23
Medium CTP2	07	070029	Unscheduled kill	213	30-Jun-94	1
Medium CTP2	07	070030	Found dead on study	538	21-May-95	19
Medium CTP2	07	070031	Found dead on study	483	27-Mar-95	
Medium CTP2	07	070032	Unscheduled kill	506	19-Apr-95	20
Medium CTP2	07	070033	Found dead on study	462	06-Mar-95	1
Medium CTP2	07	070034	Unscheduled kill	513	26-Apr-95	
Medium CTP2	07	070035	Unscheduled kill	10	09-Dec-93	
Medium CTP2	07	070036	Unscheduled kill	281	06-Sep-94	17
Medium CTP2	07	070037	Unscheduled kill	409	12-Jan-95	41
Medium CTP2	07	070038	Unscheduled kill	266	22-Aug-94	12
Medium CTP2	07	070039	Found dead on study	231	18-Jul-94	5
Medium CTP2	07	070040	Unscheduled kill	268	24-Aug-94	
Medium CTP2	07	070041	Scheduled kill	549	01-Jun-95	3
Medium CTP2	07	070042	Unscheduled kill	400	03-Jan-95	
Medium CTP2	07	070043	Unscheduled kill	508	21-Apr-95	2
Medium CTP2	07	070044	Unscheduled kill	214	01-Jul-94	
Medium CTP2	07	070045	Unscheduled kill	339	03-Nov-94	13
Medium CTP2	07	070046	Unscheduled kill	468	12-Mar-95	
Medium CTP2	07	070047	Unscheduled kill	450	22-Feb-95	30
Medium CTP2	07	070048	Scheduled kill	550	02-Jun-95	
Medium CTP2	07	070049	Unscheduled kill	472	16-Mar-95	11
Medium CTP2	07	070050	Unscheduled kill	387	21-Dec-94	
Medium CTP2	07	070051	Unscheduled kill	359	23-Nov-94	17
Medium CTP2	07	070052	Unscheduled kill	255	11-Aug-94	
Medium CTP2	07	070053	Unscheduled kill	361	25-Nov-94	22
Medium CTP2	07	070054	Unscheduled kill	452	24-Feb-95	19
Medium CTP2	07	070055	Found dead on study	477	21-Mar-95	
Medium CTP2	07	070056	Unscheduled kill	319	14-Oct-94	4
Medium CTP2	07	070057	Scheduled kill	550	02-Jun-95	1
Medium CTP2	07	070058	Unscheduled kill	211	28-Jun-94	
Medium CTP2	07	070059	Unscheduled kill	364	28-Nov-94	7
Medium CTP2	07	070060	Unscheduled kill	297	22-Sep-94	14
Medium CTP2	07	070061	Found dead on study	389	23-Dec-94	22
Medium CTP2	07	070062	Unscheduled kill	366	30-Nov-94	28

Appendix A (continued): Individual Fate of the Animals

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11
Species: Mouse
Sex : Male

Individual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
High CTP2	08	080001	Unscheduled kill	119	28-Mar-94	
High CTP2	08	080002	Found dead on study	72	09-Feb-94	
High CTP2	08	080003	Unscheduled kill	243	30-Jul-94	9
High CTP2	08	080004	Unscheduled kill	220	07-Jul-94	2
High CTP2	08	080005	Scheduled kill	274	30-Aug-94	4
High CTP2	08	080007	Scheduled kill	274	30-Aug-94	2
High CTP2	08	080008	Scheduled kill	274	30-Aug-94	
High CTP2	08	080009	Scheduled kill	274	30-Aug-94	
High CTP2	08	080010	Scheduled kill	269	25-Aug-94	
High CTP2	08	080011	Unscheduled kill	224	11-Jul-94	3
High CTP2	08	080012	Found dead on study	198	15-Jun-94	
High CTP2	08	080013	Found dead on study	251	07-Aug-94	9
High CTP2	08	080014	Unscheduled kill	144	23-Mar-94	
High CTP2	08	080015	Scheduled kill	274	30-Aug-94	
High CTP2	08	080016	Unscheduled kill	214	01-Jul-94	
High CTP2	08	080017	Scheduled kill	274	30-Aug-94	1
High CTP2	08	080018	Unscheduled kill	227	14-Jul-94	2
High CTP2	08	080019	Scheduled kill	269	25-Aug-94	
High CTP2	08	080020	Scheduled kill	274	30-Aug-94	12
High CTP2	08	080021	Scheduled kill	274	30-Aug-94	
High CTP2	08	080022	Found dead on study	238	25-Jul-94	7
High CTP2	08	080023	Scheduled kill	274	30-Aug-94	4
High CTP2	08	080024	Scheduled kill	274	30-Aug-94	11
High CTP2	08	080025	Scheduled kill	269	25-Aug-94	
High CTP2	08	080026	Scheduled kill	274	30-Aug-94	1
High CTP2	08	080027	Scheduled kill	274	30-Aug-94	11
High CTP2	08	080028	Scheduled kill	274	30-Aug-94	15
High CTP2	08	080029	Scheduled kill	274	30-Aug-94	
High CTP2	08	080030	Scheduled kill	274	30-Aug-94	17
High CTP2	08	080031	Scheduled kill	274	30-Aug-94	11
High CTP2	08	080032	Unscheduled kill	261	17-Aug-94	8
High CTP2	08	080033	Unscheduled kill	192	09-Jun-94	1
High CTP2	08	080034	Scheduled kill	274	30-Aug-94	2
High CTP2	08	080035	Scheduled kill	274	30-Aug-94	
High CTP2	08	080036	Unscheduled kill	239	26-Jul-94	7
High CTP2	08	080037	Scheduled kill	274	30-Aug-94	
High CTP2	08	080038	Scheduled kill	274	30-Aug-94	
High CTP2	08	080039	Scheduled kill	274	30-Aug-94	18
High CTP2	08	080040	Scheduled kill	269	25-Aug-94	
High CTP2	08	080041	Scheduled kill	269	25-Aug-94	
High CTP2	08	080042	Found dead on study	274	30-Aug-94	14
High CTP2	08	080043	Scheduled kill	269	25-Aug-94	
High CTP2	08	080044	Scheduled kill	274	30-Aug-94	1
High CTP2	08	080045	Scheduled kill	269	25-Aug-94	
High CTP2	08	080046	Scheduled kill	274	30-Aug-94	15
High CTP2	08	080047	Scheduled kill	274	30-Aug-94	
High CTP2	08	080048	Scheduled kill	274	30-Aug-94	
High CTP2	08	080049	Found dead on study	193	10-Jun-94	
High CTP2	08	080050	Scheduled kill	269	25-Aug-94	
High CTP2	08	080051	Unscheduled kill	171	19-May-94	
High CTP2	08	080052	Found dead on study	238	25-Jul-94	7
High CTP2	08	080053	Scheduled kill	269	25-Aug-94	
High CTP2	08	080054	Found dead on study	260	16-Aug-94	5
High CTP2	08	080055	Scheduled kill	274	30-Aug-94	15
High CTP2	08	080056	Scheduled kill	269	25-Aug-94	
High CTP2	08	080057	Unscheduled kill	267	23-Aug-94	3
High CTP2	08	080058	Scheduled kill	274	30-Aug-94	
High CTP2	08	080059	Scheduled kill	274	30-Aug-94	
High CTP2	08	080060	Scheduled kill	274	30-Aug-94	
High CTP2	08	080061	Scheduled kill	274	30-Aug-94	
High CTP2	08	080062	Unscheduled kill	171	19-May-94	

Appendix A (continued): Individual Fate of the Animals

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products (Additional Groups)
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11A
Species: Mouse
Sex : Male

Individual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
Negat. Cont.	09	090001	Found dead on study	151	17-Feb-95	
Negat. Cont.	09	090002	Scheduled kill	546	18-Mar-96	
Negat. Cont.	09	090003	Unscheduled kill	515	16-Feb-96	
Negat. Cont.	09	090004	Unscheduled kill	179	17-Mar-95	30
Negat. Cont.	09	090005	Scheduled kill	546	18-Mar-96	
Negat. Cont.	09	090006	Scheduled kill	547	19-Mar-96	
Negat. Cont.	09	090007	Unscheduled kill	478	10-Jan-96	
Negat. Cont.	09	090008	Scheduled kill	547	19-Mar-96	
Negat. Cont.	09	090009	Unscheduled kill	120	17-Jan-95	14
Negat. Cont.	09	090010	Unscheduled kill	370	24-Sep-95	1
Negat. Cont.	09	090011	Scheduled kill	547	19-Mar-96	
Negat. Cont.	09	090012	Scheduled kill	547	19-Mar-96	4
Negat. Cont.	09	090013	Scheduled kill	547	19-Mar-96	
Negat. Cont.	09	090014	Unscheduled kill	135	01-Feb-95	17
Negat. Cont.	09	090015	Found dead on study	525	26-Feb-96	
Negat. Cont.	09	090016	Scheduled kill	547	19-Mar-96	
Negat. Cont.	09	090017	Scheduled kill	547	19-Mar-96	2
Negat. Cont.	09	090018	Found dead on study	467	30-Dec-95	
Negat. Cont.	09	090019	Scheduled kill	547	19-Mar-96	
Negat. Cont.	09	090020	Found dead on study	7	26-Sep-94	
Negat. Cont.	09	090021	Scheduled kill	547	19-Mar-96	
Negat. Cont.	09	090022	Scheduled kill	547	19-Mar-96	21
Negat. Cont.	09	090023	Unscheduled kill	505	06-Feb-96	13
Negat. Cont.	09	090024	Found dead on study	518	19-Feb-96	
Negat. Cont.	09	090025	Scheduled kill	548	20-Mar-96	
Negat. Cont.	09	090026	Found dead on study	523	24-Feb-96	
Negat. Cont.	09	090027	Scheduled kill	548	20-Mar-96	1
Negat. Cont.	09	090028	Scheduled kill	548	20-Mar-96	
Negat. Cont.	09	090029	Found dead on study	525	26-Feb-96	
Negat. Cont.	09	090030	Scheduled kill	548	20-Mar-96	4
Negat. Cont.	09	090031	Scheduled kill	548	20-Mar-96	
Negat. Cont.	09	090032	Scheduled kill	548	20-Mar-96	
Negat. Cont.	09	090033	Unscheduled kill	126	23-Jan-95	16
Negat. Cont.	09	090034	Scheduled kill	548	20-Mar-96	
Negat. Cont.	09	090035	Found dead on study	515	16-Feb-96	
Negat. Cont.	09	090036	Scheduled kill	548	20-Mar-96	1
Negat. Cont.	09	090037	Scheduled kill	548	20-Mar-96	
Negat. Cont.	09	090038	Scheduled kill	549	21-Mar-96	
Negat. Cont.	09	090039	Scheduled kill	549	21-Mar-96	
Negat. Cont.	09	090040	Scheduled kill	546	18-Mar-96	
Negat. Cont.	09	090041	Scheduled kill	549	21-Mar-96	
Negat. Cont.	09	090042	Scheduled kill	549	21-Mar-96	1
Negat. Cont.	09	090043	Unscheduled kill	499	31-Jan-96	
Negat. Cont.	09	090044	Found dead on study	38	27-Oct-94	
Negat. Cont.	09	090045	Found dead on study	429	22-Nov-95	
Negat. Cont.	09	090046	Scheduled kill	549	21-Mar-96	
Negat. Cont.	09	090047	Unscheduled kill	245	22-May-95	
Negat. Cont.	09	090048	Unscheduled kill	458	21-Dec-95	
Negat. Cont.	09	090049	Unscheduled kill	479	11-Jan-96	
Negat. Cont.	09	090050	Unscheduled kill	452	15-Dec-95	
Negat. Cont.	09	090051	Scheduled kill	549	21-Mar-96	
Negat. Cont.	09	090052	Unscheduled kill	499	31-Jan-96	
Negat. Cont.	09	090053	Unscheduled kill	498	30-Jan-96	
Negat. Cont.	09	090054	Scheduled kill	546	18-Mar-96	
Negat. Cont.	09	090055	Unscheduled kill	508	09-Feb-96	
Negat. Cont.	09	090056	Scheduled kill	549	21-Mar-96	
Negat. Cont.	09	090057	Unscheduled kill	525	26-Feb-96	
Negat. Cont.	09	090058	Unscheduled kill	295	11-Jul-95	28
Negat. Cont.	09	090059	Unscheduled kill	428	21-Nov-95	35
Negat. Cont.	09	090060	Scheduled kill	546	18-Mar-96	12
Negat. Cont.	09	090061	Scheduled kill	549	21-Mar-96	
Negat. Cont.	09	090062	Scheduled kill	549	21-Mar-96	

Appendix A (continued): Individual Fate of the Animals

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products (Additional Groups)
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11A
Species: Mouse
Sex : Male

Individual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
Lower CTP1	10	100001	Scheduled kill	547	19-Mar-96	
Lower CTP1	10	100002	Unscheduled kill	542	14-Mar-96	3
Lower CTP1	10	100003	Found dead on study	532	04-Mar-96	
Lower CTP1	10	100004	Scheduled kill	547	19-Mar-96	4
Lower CTP1	10	100005	Scheduled kill	546	18-Mar-96	
Lower CTP1	10	100006	Scheduled kill	547	19-Mar-96	
Lower CTP1	10	100007	Unscheduled kill	249	26-May-95	43
Lower CTP1	10	100008	Unscheduled kill	525	26-Feb-96	
Lower CTP1	10	100009	Unscheduled kill	491	23-Jan-96	9
Lower CTP1	10	100010	Unscheduled kill	501	02-Feb-96	1
Lower CTP1	10	100011	Scheduled kill	547	19-Mar-96	
Lower CTP1	10	100012	Unscheduled kill	455	18-Dec-95	8
Lower CTP1	10	100013	Scheduled kill	547	19-Mar-96	
Lower CTP1	10	100014	Scheduled kill	547	19-Mar-96	
Lower CTP1	10	100015	Scheduled kill	547	19-Mar-96	
Lower CTP1	10	100016	Unscheduled kill	478	10-Jan-96	
Lower CTP1	10	100017	Scheduled kill	546	18-Mar-96	
Lower CTP1	10	100018	Unscheduled kill	400	24-Oct-95	
Lower CTP1	10	100019	Scheduled kill	547	19-Mar-96	
Lower CTP1	10	100020	Scheduled kill	547	19-Mar-96	1
Lower CTP1	10	100021	Unscheduled kill	527	28-Feb-96	
Lower CTP1	10	100022	Found dead on study	514	15-Feb-96	
Lower CTP1	10	100023	Unscheduled kill	487	19-Jan-96	
Lower CTP1	10	100024	Scheduled kill	547	19-Mar-96	
Lower CTP1	10	100025	Scheduled kill	548	20-Mar-96	
Lower CTP1	10	100026	Scheduled kill	548	20-Mar-96	
Lower CTP1	10	100027	Scheduled kill	548	20-Mar-96	
Lower CTP1	10	100028	Found dead on study	65	23-Nov-94	
Lower CTP1	10	100029	Scheduled kill	548	20-Mar-96	
Lower CTP1	10	100030	Found dead on study	535	07-Mar-96	
Lower CTP1	10	100031	Unscheduled kill	541	13-Mar-96	
Lower CTP1	10	100032	Scheduled kill	548	20-Mar-96	
Lower CTP1	10	100033	Unscheduled kill	378	02-Oct-95	16
Lower CTP1	10	100034	Unscheduled kill	415	08-Nov-95	28
Lower CTP1	10	100035	Scheduled kill	548	20-Mar-96	
Lower CTP1	10	100036	Scheduled kill	548	20-Mar-96	
Lower CTP1	10	100037	Scheduled kill	548	20-Mar-96	1
Lower CTP1	10	100038	Unscheduled kill	177	15-Mar-95	27
Lower CTP1	10	100039	Unscheduled kill	269	15-Jun-95	18
Lower CTP1	10	100040	Scheduled kill	548	20-Mar-96	
Lower CTP1	10	100041	Found dead on study	546	18-Mar-96	
Lower CTP1	10	100042	Scheduled kill	548	20-Mar-96	
Lower CTP1	10	100043	Scheduled kill	549	21-Mar-96	
Lower CTP1	10	100044	Found dead on study	443	06-Dec-95	
Lower CTP1	10	100045	Scheduled kill	549	21-Mar-96	
Lower CTP1	10	100046	Unscheduled kill	443	06-Dec-95	
Lower CTP1	10	100047	Scheduled kill	549	21-Mar-96	
Lower CTP1	10	100048	Scheduled kill	549	21-Mar-96	
Lower CTP1	10	100049	Scheduled kill	549	21-Mar-96	
Lower CTP1	10	100050	Unscheduled kill	445	08-Dec-95	
Lower CTP1	10	100051	Scheduled kill	546	18-Mar-96	
Lower CTP1	10	100052	Scheduled kill	546	18-Mar-96	
Lower CTP1	10	100053	Unscheduled kill	219	26-Apr-95	10
Lower CTP1	10	100054	Unscheduled kill	51	09-Nov-94	
Lower CTP1	10	100055	Scheduled kill	549	21-Mar-96	2
Lower CTP1	10	100056	Scheduled kill	549	21-Mar-96	
Lower CTP1	10	100057	Scheduled kill	549	21-Mar-96	1
Lower CTP1	10	100058	Scheduled kill	549	21-Mar-96	
Lower CTP1	10	100059	Scheduled kill	549	21-Mar-96	
Lower CTP1	10	100060	Scheduled kill	549	21-Mar-96	
Lower CTP1	10	100061	Scheduled kill	549	21-Mar-96	
Lower CTP1	10	100062	Scheduled kill	549	21-Mar-96	

ppendix A (continued): Individual Fate of the Animals

ermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products (Additional Groups)
raunhofer-Inst. f. Toxikologie u. Aerosolforsch.
tudy : 93/11A
pecies: Mouse
ex : Male

ndividual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
Lowest CTP2	11	110001	Unscheduled kill	526	27-Feb-96	37
Lowest CTP2	11	110002	Unscheduled kill	451	14-Dec-95	
Lowest CTP2	11	110003	Scheduled kill	546	18-Mar-96	
Lowest CTP2	11	110004	Unscheduled kill	165	03-Mar-95	
Lowest CTP2	11	110005	Scheduled kill	547	19-Mar-96	
Lowest CTP2	11	110006	Scheduled kill	547	19-Mar-96	
Lowest CTP2	11	110007	Unscheduled kill	497	29-Jan-96	22
Lowest CTP2	11	110008	Scheduled kill	547	19-Mar-96	
Lowest CTP2	11	110009	Unscheduled kill	514	15-Feb-96	
Lowest CTP2	11	110010	Scheduled kill	547	19-Mar-96	
Lowest CTP2	11	110011	Unscheduled kill	443	06-Dec-95	
Lowest CTP2	11	110012	Scheduled kill	547	19-Mar-96	
Lowest CTP2	11	110013	Scheduled kill	547	19-Mar-96	
Lowest CTP2	11	110014	Found dead on study	373	27-Sep-95	
Lowest CTP2	11	110015	Scheduled kill	547	19-Mar-96	
Lowest CTP2	11	110016	Scheduled kill	546	18-Mar-96	
Lowest CTP2	11	110017	Scheduled kill	547	19-Mar-96	
Lowest CTP2	11	110018	Unscheduled kill	296	12-Jul-95	21
Lowest CTP2	11	110019	Scheduled kill	547	19-Mar-96	
Lowest CTP2	11	110020	Unscheduled kill	329	14-Aug-95	11
Lowest CTP2	11	110021	Scheduled kill	547	19-Mar-96	
Lowest CTP2	11	110022	Scheduled kill	548	20-Mar-96	
Lowest CTP2	11	110023	Scheduled kill	548	20-Mar-96	
Lowest CTP2	11	110024	Scheduled kill	548	20-Mar-96	
Lowest CTP2	11	110025	Scheduled kill	548	20-Mar-96	
Lowest CTP2	11	110026	Scheduled kill	548	20-Mar-96	
Lowest CTP2	11	110027	Unscheduled kill	473	05-Jan-96	
Lowest CTP2	11	110028	Scheduled kill	548	20-Mar-96	
Lowest CTP2	11	110029	Found dead on study	224	01-May-95	
Lowest CTP2	11	110030	Scheduled kill	548	20-Mar-96	
Lowest CTP2	11	110031	Scheduled kill	548	20-Mar-96	
Lowest CTP2	11	110032	Scheduled kill	546	18-Mar-96	
Lowest CTP2	11	110033	Unscheduled kill	282	28-Jun-95	2
Lowest CTP2	11	110034	Scheduled kill	548	20-Mar-96	
Lowest CTP2	11	110035	Scheduled kill	548	20-Mar-96	
Lowest CTP2	11	110036	Scheduled kill	546	18-Mar-96	
Lowest CTP2	11	110037	Unscheduled kill	462	25-Dec-95	
Lowest CTP2	11	110038	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110039	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110040	Unscheduled kill	492	24-Jan-96	
Lowest CTP2	11	110041	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110042	Found dead on study	427	20-Nov-95	
Lowest CTP2	11	110043	Unscheduled kill	527	28-Feb-96	
Lowest CTP2	11	110044	Found dead on study	459	22-Dec-95	
Lowest CTP2	11	110045	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110046	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110047	Unscheduled kill	527	28-Feb-96	
Lowest CTP2	11	110048	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110049	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110050	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110051	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110052	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110053	Unscheduled kill	450	13-Dec-95	
Lowest CTP2	11	110054	Scheduled kill	546	18-Mar-96	2
Lowest CTP2	11	110055	Unscheduled kill	445	08-Dec-95	
Lowest CTP2	11	110056	Found dead on study	541	13-Mar-96	
Lowest CTP2	11	110057	Unscheduled kill	518	19-Feb-96	8
Lowest CTP2	11	110058	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110059	Unscheduled kill	427	20-Nov-95	
Lowest CTP2	11	110060	Unscheduled kill	529	01-Mar-96	14
Lowest CTP2	11	110061	Scheduled kill	549	21-Mar-96	
Lowest CTP2	11	110062	Found dead on study	530	02-Mar-96	

Appendix A (continued): Individual Fate of the Animals

Dermal Carcinogenicity Study (78 wks) of 2 Coal Tar Products (Additional Groups)
Fraunhofer-Inst. f. Toxikologie u. Aerosolforsch.
Study : 93/11A
Species: Mouse
Sex : Male

Individual Animal Death Report

Dose	Group	Animal	Manner of death	Nominal study day of death	Date of death	No. of times treatment was interrupted for
Lower CTP2	12	120001	Unscheduled kill	245	22-May-95	14
Lower CTP2	12	120002	Scheduled kill	546	18-Mar-96	4
Lower CTP2	12	120003	Scheduled kill	546	18-Mar-96	12
Lower CTP2	12	120004	Unscheduled kill	262	08-Jun-95	35
Lower CTP2	12	120005	Scheduled kill	546	18-Mar-96	
Lower CTP2	12	120006	Unscheduled kill	490	22-Jan-96	1
Lower CTP2	12	120007	Scheduled kill	547	19-Mar-96	
Lower CTP2	12	120008	Scheduled kill	547	19-Mar-96	
Lower CTP2	12	120009	Found dead on study	261	07-Jun-95	
Lower CTP2	12	120010	Found dead on study	126	23-Jan-95	
Lower CTP2	12	120011	Scheduled kill	547	19-Mar-96	
Lower CTP2	12	120012	Scheduled kill	547	19-Mar-96	
Lower CTP2	12	120013	Found dead on study	428	21-Nov-95	
Lower CTP2	12	120014	Scheduled kill	547	19-Mar-96	
Lower CTP2	12	120015	Scheduled kill	547	19-Mar-96	
Lower CTP2	12	120016	Scheduled kill	547	19-Mar-96	
Lower CTP2	12	120017	Scheduled kill	547	19-Mar-96	
Lower CTP2	12	120018	Scheduled kill	546	18-Mar-96	
Lower CTP2	12	120019	Scheduled kill	547	19-Mar-96	
Lower CTP2	12	120020	Scheduled kill	547	19-Mar-96	
Lower CTP2	12	120021	Unscheduled kill	255	01-Jun-95	19
Lower CTP2	12	120022	Scheduled kill	546	18-Mar-96	
Lower CTP2	12	120023	Unscheduled kill	466	29-Dec-95	
Lower CTP2	12	120024	Scheduled kill	548	20-Mar-96	
Lower CTP2	12	120025	Scheduled kill	548	20-Mar-96	
Lower CTP2	12	120026	Unscheduled kill	494	26-Jan-96	
Lower CTP2	12	120027	Scheduled kill	548	20-Mar-96	2
Lower CTP2	12	120028	Scheduled kill	548	20-Mar-96	
Lower CTP2	12	120029	Unscheduled kill	120	17-Jan-95	11
Lower CTP2	12	120030	Scheduled kill	548	20-Mar-96	9
Lower CTP2	12	120031	Scheduled kill	548	20-Mar-96	
Lower CTP2	12	120032	Scheduled kill	548	20-Mar-96	
Lower CTP2	12	120033	Scheduled kill	548	20-Mar-96	
Lower CTP2	12	120034	Scheduled kill	548	20-Mar-96	
Lower CTP2	12	120035	Scheduled kill	549	21-Mar-96	
Lower CTP2	12	120036	Unscheduled kill	385	09-Oct-95	
Lower CTP2	12	120037	Unscheduled kill	381	05-Oct-95	26
Lower CTP2	12	120038	Scheduled kill	549	21-Mar-96	
Lower CTP2	12	120039	Found dead on study	538	10-Mar-96	
Lower CTP2	12	120040	Unscheduled kill	497	29-Jan-96	
Lower CTP2	12	120041	Found dead on study	524	25-Feb-96	
Lower CTP2	12	120042	Scheduled kill	549	21-Mar-96	
Lower CTP2	12	120043	Unscheduled kill	535	07-Mar-96	
Lower CTP2	12	120044	Scheduled kill	549	21-Mar-96	
Lower CTP2	12	120045	Unscheduled kill	483	15-Jan-96	
Lower CTP2	12	120046	Scheduled kill	549	21-Mar-96	
Lower CTP2	12	120047	Unscheduled kill	290	06-Jul-95	18
Lower CTP2	12	120048	Unscheduled kill	228	05-May-95	33
Lower CTP2	12	120049	Scheduled kill	549	21-Mar-96	
Lower CTP2	12	120050	Found dead on study	504	05-Feb-96	
Lower CTP2	12	120051	Found dead on study	440	03-Dec-95	
Lower CTP2	12	120052	Unscheduled kill	502	03-Feb-96	
Lower CTP2	12	120053	Unscheduled kill	441	04-Dec-95	
Lower CTP2	12	120054	Scheduled kill	549	21-Mar-96	
Lower CTP2	12	120055	Unscheduled kill	501	02-Feb-96	5
Lower CTP2	12	120056	Unscheduled kill	469	01-Jan-96	
Lower CTP2	12	120057	Found dead on study	544	16-Mar-96	4
Lower CTP2	12	120058	Unscheduled kill	312	28-Jul-95	6
Lower CTP2	12	120059	Unscheduled kill	408	01-Nov-95	
Lower CTP2	12	120060	Unscheduled kill	471	03-Jan-96	
Lower CTP2	12	120061	Unscheduled kill	228	05-May-95	27
Lower CTP2	12	120062	Found dead on study	466	29-Dec-95	

Appendix A1: Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = Negat.Cont.

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumor
010008	11	Unscheduled kill	,9839	,0160	1	61	no
010052	45	Found death on study	,9677	,0224	2	60	no
010038	204	Found death on study	,9516	,0273	3	59	no
010023	254	Unscheduled kill	,9355	,0312	4	58	no
010018	291	Unscheduled kill	,9194	,0346	5	57	no
010031	364	Unscheduled kill	,9032	,0375	6	56	no
010044	365	Found death on study	,8871	,0402	7	55	no
010015	401	Found death on study	,8710	,0426	8	54	no
010037	435	Unscheduled kill	,8548	,0447	9	53	no
010005	439	Found death on study	,8387	,0467	10	52	no
010062	449	Unscheduled kill	,8226	,0485	11	51	no
010047	466	Unscheduled kill	,8065	,0502	12	50	no
010009	472	Unscheduled kill	,7903	,0517	13	49	no
010029	479	Unscheduled kill	,7742	,0531	14	48	no
010022	483	Unscheduled kill	,7581	,0544	15	47	no
010016	484	Found death on study	,7419	,0556	16	46	no
010046	492	Unscheduled kill	,7258	,0567	17	45	no
010061	503	Found death on study	,7097	,0576	18	44	no
010032	512	Unscheduled kill	,6935	,0585	19	43	yes
010026	514	Found death on study	,6774	,0594	20	42	no
010035	515	Found death on study			21	41	no
010059	515	Unscheduled kill	,6452	,0608	22	40	no
010011	517	Found death on study	,6290	,0613	23	39	no
010030	532	Found death on study	,6129	,0619	24	38	no
010024	543	Unscheduled kill	,5968	,0623	25	37	no
010049	545	Found death on study	,5806	,0627	26	36	no
010001	546	Scheduled kill			26	35	no
010002	546	Scheduled kill			26	34	no
010003	546	Scheduled kill			26	33	no
010004	547	Scheduled kill			26	32	no
010006	547	Scheduled kill			26	31	no
010007	547	Scheduled kill			26	30	no
010010	547	Scheduled kill			26	29	no
010012	547	Scheduled kill			26	28	no
010013	547	Scheduled kill			26	27	no
010014	547	Scheduled kill			26	26	no
010017	547	Scheduled kill			26	25	no
010019	547	Scheduled kill			26	24	no
010020	548	Scheduled kill			26	23	no
010021	548	Scheduled kill			26	22	no
010025	548	Scheduled kill			26	21	no
010027	548	Scheduled kill			26	20	no
010028	548	Scheduled kill			26	19	no
010033	548	Scheduled kill			26	18	no
010034	548	Scheduled kill			26	17	no
010036	548	Scheduled kill			26	16	no
010039	549	Scheduled kill			26	15	no
010040	549	Scheduled kill			26	14	no
010041	549	Scheduled kill			26	13	no
010042	549	Scheduled kill			26	12	no
010043	549	Scheduled kill			26	11	no
010045	549	Scheduled kill			26	10	no
010048	549	Scheduled kill			26	9	no
010050	549	Scheduled kill			26	8	no
010051	549	Scheduled kill			26	7	no
010053	549	Scheduled kill			26	6	no
010054	549	Scheduled kill			26	5	no
010055	550	Scheduled kill			26	4	no
010056	550	Scheduled kill			26	3	no
010057	550	Scheduled kill			26	2	no
010058	550	Scheduled kill			26	1	no
010060	550	Scheduled kill			26	0	no

Number of Cases: 62 Censored: 36 (58,06%) Events: 26

Appendix A1 (continued): Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = Posit.Cont.

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumor
020014	261	Unscheduled kill	.9839	.0160	1	61	no
020008	303	Unscheduled kill	.9677	.0224	2	60	yes
020050	309	Found death on study	.9516	.0273	3	59	no
020059	322	Unscheduled kill	.9355	.0312	4	58	no
020027	345	Unscheduled kill	.9194	.0346	5	57	yes
020028	351	Unscheduled kill	.9032	.0375	6	56	yes
020053	356	Found death on study	.8871	.0402	7	55	yes
020001	366	Unscheduled kill	.8710	.0426	8	54	yes
020054	378	Unscheduled kill	.8548	.0447	9	53	yes
020061	380	Found death on study	.8387	.0467	10	52	yes
020006	389	Found death on study	.8226	.0485	11	51	yes
020056	395	Unscheduled kill	.8065	.0502	12	50	yes
020035	414	Found death on study	.7903	.0517	13	49	no
020055	415	Unscheduled kill	.7742	.0531	14	48	no
020021	421	Unscheduled kill	.7581	.0544	15	47	yes
020049	429	Found death on study	.7419	.0556	16	46	yes
020045	437	Unscheduled kill	.7258	.0567	17	45	yes
020011	438	Unscheduled kill	.7097	.0576	18	44	yes
020007	444	Unscheduled kill	.6935	.0585	19	43	no
020004	448	Unscheduled kill			20	42	yes
020020	448	Found death on study	.6613	.0601	21	41	no
020025	452	Unscheduled kill	.6452	.0608	22	40	yes
020015	454	Found death on study	.6290	.0613	23	39	no
020031	455	Unscheduled kill	.6129	.0619	24	38	yes
020010	463	Unscheduled kill	.5968	.0623	25	37	yes
020034	465	Unscheduled kill	.5806	.0627	26	36	yes
020051	471	Unscheduled kill	.5645	.0630	27	35	yes
020060	483	Unscheduled kill	.5484	.0632	28	34	yes
020013	487	Unscheduled kill	.5323	.0634	29	33	yes
020046	491	Unscheduled kill	.5161	.0635	30	32	yes
020052	505	Unscheduled kill	.5000	.0635	31	31	yes
020039	511	Unscheduled kill			32	30	yes
020041	511	Unscheduled kill	.4677	.0634	33	29	yes
020038	514	Found death on study	.4516	.0632	34	28	yes
020057	519	Unscheduled kill	.4355	.0630	35	27	yes
020043	525	Unscheduled kill	.4194	.0627	36	26	yes
020005	527	Unscheduled kill	.4032	.0623	37	25	yes
020002	546	Scheduled kill			37	24	yes
020003	546	Scheduled kill			37	23	no
020009	546	Scheduled kill			37	22	no
020012	547	Scheduled kill			37	21	yes
020016	547	Scheduled kill			37	20	no
020017	547	Scheduled kill			37	19	yes
020018	547	Scheduled kill			37	18	no
020019	547	Scheduled kill			37	17	yes
020022	547	Scheduled kill			37	16	yes
020023	548	Scheduled kill			37	15	no
020024	548	Scheduled kill			37	14	yes
020026	548	Scheduled kill			37	13	yes
020029	548	Scheduled kill			37	12	yes
020030	548	Scheduled kill			37	11	yes
020032	548	Scheduled kill			37	10	yes
020033	549	Scheduled kill			37	9	yes
020036	549	Scheduled kill			37	8	yes
020037	549	Scheduled kill			37	7	yes
020040	549	Scheduled kill			37	6	yes
020042	549	Scheduled kill			37	5	yes
020044	549	Scheduled kill			37	4	no
020047	550	Scheduled kill			37	3	no
020048	550	Scheduled kill			37	2	yes
020058	550	Scheduled kill			37	1	yes
020062	550	Scheduled kill			37	0	yes

Number of Cases: 62 Censored: 25 (40,32%) Events: 37

Appendix A1 (continued): Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = Low CTP1

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumor
030039	248	Found death on study	,9839	,0160	1	61	no
030050	312	Unscheduled kill	,9677	,0224	2	60	no
030025	317	Unscheduled kill	,9516	,0273	3	59	no
030033	319	Unscheduled kill	,9355	,0312	4	58	no
030053	339	Unscheduled kill	,9194	,0346	5	57	no
030003	345	Unscheduled kill	,9032	,0375	6	56	no
030046	373	Unscheduled kill	,8871	,0402	7	55	no
030045	381	Unscheduled kill	,8710	,0426	8	54	no
030049	398	Found death on study	,8548	,0447	9	53	no
030056	409	Unscheduled kill	,8387	,0467	10	52	no
030009	414	Found death on study			11	51	no
030047	414	Unscheduled kill			12	50	no
030057	414	Unscheduled kill	,7903	,0517	13	49	no
030005	415	Unscheduled kill	,7742	,0531	14	48	no
030001	416	Found death on study			15	47	no
030004	416	Unscheduled kill	,7419	,0556	16	46	no
030061	424	Unscheduled kill	,7258	,0567	17	45	no
030013	438	Unscheduled kill	,7097	,0576	18	44	no
030021	440	Found death on study	,6935	,0585	19	43	no
030034	441	Unscheduled kill	,6774	,0594	20	42	no
030007	442	Unscheduled kill	,6613	,0601	21	41	no
030062	452	Unscheduled kill	,6452	,0608	22	40	no
030020	461	Found death on study	,6290	,0613	23	39	no
030024	470	Unscheduled kill	,6129	,0619	24	38	no
030035	471	Unscheduled kill	,5968	,0623	25	37	no
030026	484	Unscheduled kill	,5806	,0627	26	36	no
030017	491	Unscheduled kill	,5645	,0630	27	35	no
030040	496	Found death on study	,5484	,0632	28	34	no
030060	497	Found death on study	,5323	,0634	29	33	no
030055	505	Unscheduled kill	,5161	,0635	30	32	no
030030	528	Unscheduled kill			31	31	no
030051	528	Unscheduled kill	,4839	,0635	32	30	no
030002	534	Unscheduled kill	,4677	,0634	33	29	no
030037	535	Unscheduled kill	,4516	,0632	34	28	no
030006	546	Scheduled kill			34	27	no
030008	546	Scheduled kill			34	26	no
030010	546	Scheduled kill			34	25	no
030011	547	Scheduled kill			34	24	no
030012	547	Scheduled kill			34	23	no
030014	547	Scheduled kill			34	22	no
030015	547	Scheduled kill			34	21	no
030016	547	Scheduled kill			34	20	no
030018	547	Scheduled kill			34	19	no
030019	548	Scheduled kill			34	18	no
030022	548	Scheduled kill			34	17	no
030023	548	Scheduled kill			34	16	no
030027	548	Scheduled kill			34	15	no
030028	548	Scheduled kill			34	14	no
030029	548	Scheduled kill			34	13	no
030031	548	Scheduled kill			34	12	no
030032	549	Scheduled kill			34	11	no
030036	549	Scheduled kill			34	10	no
030038	549	Scheduled kill			34	9	no
030041	549	Scheduled kill			34	8	no
030042	549	Scheduled kill			34	7	no
030043	549	Scheduled kill			34	6	no
030044	549	Scheduled kill			34	5	no
030048	549	Scheduled kill			34	4	no
030052	550	Scheduled kill			34	3	no
030054	550	Scheduled kill			34	2	no
030058	550	Scheduled kill			34	1	no
030059	550	Scheduled kill			34	0	no

Number of Cases: 62 Censored: 28 (45,16%) Events: 34

Appendix A1 (continued): Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = Medium CTP1

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumor
040040	172	Unscheduled kill	.9839	.0160	1	61	no
040032	225	Found death on study	.9677	.0224	2	60	no
040017	228	Found death on study	.9516	.0273	3	59	no
040044	232	Unscheduled kill	.9355	.0312	4	58	no
040060	234	Unscheduled kill	.9194	.0346	5	57	no
040058	261	Unscheduled kill	.9032	.0375	6	56	no
040036	269	Unscheduled kill	.8871	.0402	7	55	no
040037	317	Unscheduled kill	.8710	.0426	8	54	no
040008	340	Unscheduled kill	.8548	.0447	9	53	no
040047	346	Unscheduled kill	.8387	.0467	10	52	no
040039	395	Unscheduled kill			11	51	no
040050	395	Unscheduled kill	.8065	.0502	12	50	no
040020	396	Unscheduled kill	.7903	.0517	13	49	no
040016	400	Unscheduled kill	.7742	.0531	14	48	no
040028	406	Unscheduled kill	.7581	.0544	15	47	no
040006	420	Unscheduled kill	.7419	.0556	16	46	no
040023	421	Unscheduled kill	.7258	.0567	17	45	no
040043	422	Unscheduled kill	.7097	.0576	18	44	no
040010	453	Found death on study	.6935	.0585	19	43	no
040014	457	Unscheduled kill	.6774	.0594	20	42	no
040059	463	Unscheduled kill	.6613	.0601	21	41	no
040009	469	Unscheduled kill	.6452	.0608	22	40	no
040049	473	Found death on study	.6290	.0613	23	39	no
040027	487	Unscheduled kill	.6129	.0619	24	38	no
040003	490	Found death on study	.5968	.0623	25	37	no
040022	497	Found death on study	.5806	.0627	26	36	no
040041	500	Found death on study	.5645	.0630	27	35	no
040046	506	Unscheduled kill	.5484	.0632	28	34	yes
040007	512	Unscheduled kill	.5323	.0634	29	33	no
040025	519	Unscheduled kill	.5161	.0635	30	32	no
040057	520	Unscheduled kill	.5000	.0635	31	31	no
040021	535	Unscheduled kill	.4839	.0635	32	30	no
040052	538	Found death on study			33	29	no
040054	538	Found death on study	.4516	.0632	34	28	no
040048	541	Found death on study	.4355	.0630	35	27	no
040031	545	Unscheduled kill	.4194	.0627	36	26	no
040001	546	Scheduled kill			36	25	no
040002	546	Scheduled kill			36	24	no
040004	546	Scheduled kill			36	23	no
040005	547	Scheduled kill			36	22	no
040011	547	Scheduled kill			36	21	no
040012	547	Scheduled kill			36	20	no
040013	547	Scheduled kill			36	19	no
040015	547	Scheduled kill			36	18	no
040018	547	Scheduled kill			36	17	no
040019	548	Scheduled kill			36	16	no
040024	548	Scheduled kill			36	15	no
040026	548	Scheduled kill			36	14	no
040029	548	Scheduled kill			36	13	no
040030	548	Scheduled kill			36	12	no
040033	548	Scheduled kill			36	11	no
040034	549	Scheduled kill			36	10	no
040035	549	Scheduled kill			36	9	no
040038	549	Scheduled kill			36	8	no
040042	549	Scheduled kill			36	7	no
040045	549	Scheduled kill			36	6	no
040051	549	Scheduled kill			36	5	no
040053	549	Scheduled kill			36	4	no
040055	550	Scheduled kill			36	3	no
040056	550	Scheduled kill			36	2	no
040061	550	Scheduled kill			36	1	no
040062	550	Scheduled kill			36	0	no

Number of Cases: 62 Censored: 26 (41.94%) Events: 36

Appendix A1 (continued): Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = High CTP1

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumor
050040	214	Unscheduled kill	,9839	,0160	1	61	no
050006	219	Unscheduled kill	,9677	,0224	2	60	no
050061	230	Found death on study	,9516	,0273	3	59	no
050003	241	Unscheduled kill	,9355	,0312	4	58	no
050031	247	Unscheduled kill	,9194	,0346	5	57	no
050022	256	Unscheduled kill			6	56	no
050056	256	Unscheduled kill	,8871	,0402	7	55	no
050033	261	Unscheduled kill	,8710	,0426	8	54	no
050060	305	Unscheduled kill	,8548	,0447	9	53	no
050029	312	Unscheduled kill	,8387	,0467	10	52	no
050044	340	Unscheduled kill	,8226	,0485	11	51	no
050043	344	Found death on study	,8065	,0502	12	50	no
050011	346	Unscheduled kill	,7903	,0517	13	49	no
050012	347	Unscheduled kill	,7742	,0531	14	48	no
050059	368	Unscheduled kill	,7581	,0544	15	47	no
050007	384	Found death on study	,7419	,0556	16	46	no
050026	385	Found death on study	,7258	,0567	17	45	no
050009	388	Unscheduled kill	,7097	,0576	18	44	no
050037	389	Found death on study	,6935	,0585	19	43	no
050038	396	Unscheduled kill	,6774	,0594	20	42	no
050054	402	Unscheduled kill	,6613	,0601	21	41	no
050036	415	Unscheduled kill	,6452	,0608	22	40	no
050002	416	Unscheduled kill	,6290	,0613	23	39	no
050004	417	Unscheduled kill	,6129	,0619	24	38	no
050013	421	Unscheduled kill	,5968	,0623	25	37	no
050027	448	Found death on study	,5806	,0627	26	36	no
050032	450	Unscheduled kill	,5645	,0630	27	35	no
050024	452	Unscheduled kill	,5484	,0632	28	34	no
050041	464	Unscheduled kill	,5323	,0634	29	33	no
050014	467	Found death on study	,5161	,0635	30	32	no
050023	469	Unscheduled kill	,5000	,0635	31	31	no
050035	481	Found death on study	,4839	,0635	32	30	no
050049	484	Found death on study	,4677	,0634	33	29	no
050001	490	Unscheduled kill	,4516	,0632	34	28	no
050010	494	Unscheduled kill	,4355	,0630	35	27	no
050052	498	Unscheduled kill	,4194	,0627	36	26	no
050055	525	Scheduled kill			36	25	no
050042	529	Unscheduled kill	,4026	,0624	37	24	no
050020	536	Unscheduled kill	,3858	,0620	38	23	yes
050046	539	Unscheduled kill	,3690	,0615	39	22	no
050039	543	Unscheduled kill	,3523	,0610	40	21	no
050019	546	Found death on study	,3355	,0603	41	20	no
050005	546	Scheduled kill			41	19	no
050008	546	Scheduled kill			41	18	no
050015	546	Scheduled kill			41	17	no
050016	547	Scheduled kill			41	16	no
050017	547	Scheduled kill			41	15	no
050018	547	Scheduled kill			41	14	no
050021	547	Scheduled kill			41	13	no
050025	547	Scheduled kill			41	12	no
050028	547	Scheduled kill			41	11	no
050030	548	Scheduled kill			41	10	no
050034	548	Scheduled kill			41	9	no
050045	548	Scheduled kill			41	8	no
050047	548	Scheduled kill			41	7	no
050048	548	Scheduled kill			41	6	no
050050	549	Scheduled kill			41	5	no
050051	549	Scheduled kill			41	4	yes
050053	549	Scheduled kill			41	3	no
050057	549	Scheduled kill			41	2	no
050058	550	Scheduled kill			41	1	no
050062	550	Scheduled kill			41	0	no

Number of Cases: 62 Censored: 21 (33,87%) Events: 41

Appendix A1 (continued): Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = Low CTP2

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumor
060058	16	Found death on study	,9839	,0160	1	61	no
060020	39	Unscheduled kill	,9677	,0224	2	60	no
060004	59	Found death on study	,9516	,0273	3	59	no
060023	210	Unscheduled kill	,9355	,0312	4	58	no
060032	229	Unscheduled kill	,9194	,0346	5	57	no
060005	247	Found death on study			6	56	no
060059	247	Unscheduled kill	,8871	,0402	7	55	no
060018	255	Unscheduled kill			8	54	no
060025	255	Unscheduled kill	,8548	,0447	9	53	no
060015	297	Found death on study	,8387	,0467	10	52	no
060003	336	Unscheduled kill	,8226	,0485	11	51	no
060041	358	Unscheduled kill	,8065	,0502	12	50	no
060021	366	Found death on study	,7903	,0517	13	49	no
060062	368	Unscheduled kill	,7742	,0531	14	48	no
060030	371	Unscheduled kill	,7581	,0544	15	47	no
060029	379	Found death on study	,7419	,0556	16	46	no
060051	387	Unscheduled kill	,7258	,0567	17	45	no
060049	388	Unscheduled kill	,7097	,0576	18	44	no
060044	389	Unscheduled kill	,6935	,0585	19	43	no
060061	393	Unscheduled kill	,6774	,0594	20	42	no
060053	406	Unscheduled kill	,6613	,0601	21	41	no
060002	412	Found death on study	,6452	,0608	22	40	no
060012	417	Unscheduled kill	,6290	,0613	23	39	no
060013	428	Unscheduled kill	,6129	,0619	24	38	no
060036	445	Unscheduled kill	,5968	,0623	25	37	yes
060048	468	Found death on study	,5806	,0627	26	36	no
060047	475	Unscheduled kill	,5645	,0630	27	35	no
060010	482	Found death on study	,5484	,0632	28	34	no
060060	487	Found death on study	,5323	,0634	29	33	yes
060057	490	Scheduled kill			29	32	no
060034	502	Found death on study	,5156	,0635	30	31	no
060014	511	Found death on study			31	30	no
060054	511	Unscheduled kill	,4824	,0636	32	29	no
060033	514	Unscheduled kill	,4657	,0636	33	28	no
060035	522	Unscheduled kill	,4491	,0634	34	27	yes
060043	536	Unscheduled kill	,4325	,0632	35	26	no
060052	537	Unscheduled kill	,4158	,0630	36	25	yes
060027	543	Unscheduled kill	,3992	,0626	37	24	no
060001	546	Scheduled kill			37	23	no
060006	546	Scheduled kill			37	22	yes
060007	546	Scheduled kill			37	21	no
060008	547	Scheduled kill			37	20	no
060009	547	Scheduled kill			37	19	yes
060011	547	Scheduled kill			37	18	no
060016	547	Scheduled kill			37	17	yes
060017	547	Scheduled kill			37	16	no
060019	547	Scheduled kill			37	15	no
060024	548	Found death on study	,3726	,0638	38	14	no
060022	548	Scheduled kill			38	13	no
060026	548	Scheduled kill			38	12	no
060028	548	Scheduled kill			38	11	no
060031	548	Scheduled kill			38	10	no
060037	548	Scheduled kill			38	9	yes
060038	548	Scheduled kill			38	8	no
060039	549	Scheduled kill			38	7	yes
060040	549	Scheduled kill			38	6	no
060042	549	Scheduled kill			38	5	no
060045	549	Scheduled kill			38	4	no
060046	550	Scheduled kill			38	3	no
060050	550	Scheduled kill			38	2	no
060055	550	Scheduled kill			38	1	no
060056	550	Scheduled kill			38	0	no

Number of Cases: 62 Censored: 24 (38,71%) Events: 38

Appendix A1 (continued): Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = Medium CTP2

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumors
070035	10	Unscheduled kill	,9839	,0160	1	61	no
070008	157	Unscheduled kill	,9677	,0224	2	60	no
070058	211	Unscheduled kill	,9516	,0273	3	59	no
070029	213	Unscheduled kill	,9355	,0312	4	58	no
070044	214	Unscheduled kill	,9194	,0346	5	57	no
070039	231	Found death on study	,9032	,0375	6	56	no
070052	255	Unscheduled kill	,8871	,0402	7	55	no
070001	261	Unscheduled kill	,8710	,0426	8	54	no
070038	266	Unscheduled kill	,8548	,0447	9	53	no
070040	268	Unscheduled kill	,8387	,0467	10	52	no
070036	281	Unscheduled kill	,8226	,0485	11	51	no
070060	297	Unscheduled kill	,8065	,0502	12	50	no
070007	299	Found death on study	,7903	,0517	13	49	no
070016	305	Unscheduled kill	,7742	,0531	14	48	no
070056	319	Unscheduled kill	,7581	,0544	15	47	no
070045	339	Unscheduled kill	,7419	,0556	16	46	no
070013	347	Unscheduled kill	,7258	,0567	17	45	no
070004	355	Found death on study	,7097	,0576	18	44	no
070051	359	Unscheduled kill	,6935	,0585	19	43	no
070053	361	Unscheduled kill	,6774	,0594	20	42	yes
070059	364	Unscheduled kill	,6613	,0601	21	41	no
070062	366	Unscheduled kill	,6452	,0608	22	40	no
070019	380	Unscheduled kill	,6290	,0613	23	39	no
070028	382	Unscheduled kill	,6129	,0619	24	38	no
070050	387	Unscheduled kill	,5968	,0623	25	37	no
070061	389	Found death on study	,5806	,0627	26	36	yes
070027	396	Unscheduled kill	,5645	,0630	27	35	yes
070042	400	Unscheduled kill	,5484	,0632	28	34	yes
070037	409	Unscheduled kill	,5323	,0634	29	33	no
070017	413	Unscheduled kill	,5161	,0635	30	32	no
070026	417	Unscheduled kill	,5000	,0635	31	31	no
070003	420	Unscheduled kill	,4839	,0635	32	30	yes
070022	421	Unscheduled kill	,4677	,0634	33	29	no
070015	424	Unscheduled kill	,4516	,0632	34	28	no
070011	436	Unscheduled kill	,4355	,0630	35	27	yes
070012	443	Unscheduled kill	,4194	,0627	36	26	yes
070047	450	Unscheduled kill	,4032	,0623	37	25	no
070054	452	Unscheduled kill	,3871	,0619	38	24	no
070010	456	Found death on study	,3710	,0613	39	23	no
070033	462	Found death on study	,3548	,0608	40	22	yes
070046	468	Unscheduled kill	,3387	,0601	41	21	yes
070049	472	Unscheduled kill	,3226	,0594	42	20	no
070055	477	Found death on study	,3065	,0585	43	19	yes
070031	483	Found death on study	,2903	,0576	44	18	no
070032	506	Unscheduled kill	,2742	,0567	45	17	yes
070043	508	Unscheduled kill	,2581	,0556	46	16	no
070034	513	Unscheduled kill	,2419	,0544	47	15	yes
070025	521	Unscheduled kill	,2258	,0531	48	14	yes
070020	533	Unscheduled kill	,2097	,0517	49	13	yes
070030	538	Found death on study	,1935	,0502	50	12	no
070009	541	Unscheduled kill	,1774	,0485	51	11	yes
070002	547	Scheduled kill			51	10	yes
070005	547	Scheduled kill			51	9	yes
070006	547	Scheduled kill			51	8	yes
070014	548	Scheduled kill			51	7	yes
070018	548	Scheduled kill			51	6	no
070021	548	Scheduled kill			51	5	yes
070023	549	Scheduled kill			51	4	yes
070024	549	Scheduled kill			51	3	no
070041	549	Scheduled kill			51	2	yes
070048	550	Scheduled kill			51	1	no
070057	550	Scheduled kill			51	0	yes

Number of Cases: 62 Censored: 11 (17,74%) Events: 51

Appendix A1 (continued): Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = High CTP2

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumor
080002	72	Found death on study	,9836	,0163	1	60	no
080014	114	Unscheduled kill	,9672	,0228	2	59	no
080001	119	Unscheduled kill	,9508	,0277	3	58	no
080051	171	Unscheduled kill			4	57	no
080062	171	Unscheduled kill	,9180	,0351	5	56	no
080033	192	Unscheduled kill	,9016	,0381	6	55	no
080049	193	Found death on study	,8852	,0408	7	54	no
080012	198	Found death on study	,8689	,0432	8	53	yes
080016	214	Unscheduled kill	,8525	,0454	9	52	no
080004	220	Unscheduled kill	,8361	,0474	10	51	no
080011	224	Unscheduled kill	,8197	,0492	11	50	no
080018	227	Unscheduled kill	,8033	,0509	12	49	no
080022	238	Found death on study			13	48	no
080052	238	Found death on study	,7705	,0538	14	47	yes
080036	239	Unscheduled kill	,7541	,0551	15	46	no
080003	243	Unscheduled kill	,7377	,0563	16	45	no
080013	251	Found death on study	,7213	,0574	17	44	no
080054	260	Found death on study	,7049	,0584	18	43	no
080032	261	Unscheduled kill	,6885	,0593	19	42	no
080057	267	Unscheduled kill	,6721	,0601	20	41	no
080010	269	Scheduled kill			20	40	no
080019	269	Scheduled kill			20	39	no
080025	269	Scheduled kill			20	38	no
080040	269	Scheduled kill			20	37	yes
080041	269	Scheduled kill			20	36	no
080043	269	Scheduled kill			20	35	no
080045	269	Scheduled kill			20	34	yes
080050	269	Scheduled kill			20	33	no
080053	269	Scheduled kill			20	32	no
080056	269	Scheduled kill			20	31	no
080042	274	Found death on study	,6504	,0620	21	30	no
080005	274	Scheduled kill			21	29	no
080007	274	Scheduled kill			21	28	no
080008	274	Scheduled kill			21	27	yes
080009	274	Scheduled kill			21	26	yes
080015	274	Scheduled kill			21	25	yes
080017	274	Scheduled kill			21	24	no
080020	274	Scheduled kill			21	23	no
080021	274	Scheduled kill			21	22	yes
080023	274	Scheduled kill			21	21	no
080024	274	Scheduled kill			21	20	no
080026	274	Scheduled kill			21	19	yes
080027	274	Scheduled kill			21	18	no
080028	274	Scheduled kill			21	17	no
080029	274	Scheduled kill			21	16	yes
080030	274	Scheduled kill			21	15	no
080031	274	Scheduled kill			21	14	no
080034	274	Scheduled kill			21	13	no
080035	274	Scheduled kill			21	12	yes
080037	274	Scheduled kill			21	11	yes
080038	274	Scheduled kill			21	10	yes
080039	274	Scheduled kill			21	9	no
080044	274	Scheduled kill			21	8	yes
080046	274	Scheduled kill			21	7	no
080047	274	Scheduled kill			21	6	yes
080048	274	Scheduled kill			21	5	yes
080055	274	Scheduled kill			21	4	yes
080058	274	Scheduled kill			21	3	no
080059	274	Scheduled kill			21	2	yes
080060	274	Scheduled kill			21	1	yes
080061	274	Scheduled kill			21	0	yes

Number of Cases: 61 Censored: 40 (65,57%) Events: 21

Appendix A1 (continued): Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = Negat.Cont. A

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumor
090020	7	Found death on study	,9839	,0160	1	61	no
090044	38	Found death on study	,9677	,0224	2	60	no
090009	120	Unscheduled kill	,9516	,0273	3	59	no
090033	126	Unscheduled kill	,9355	,0312	4	58	no
090014	135	Unscheduled kill	,9194	,0346	5	57	no
090001	151	Found death on study	,9032	,0375	6	56	no
090004	179	Unscheduled kill	,8871	,0402	7	55	no
090047	245	Unscheduled kill	,8710	,0426	8	54	no
090058	295	Unscheduled kill	,8548	,0447	9	53	no
090010	370	Unscheduled kill	,8387	,0467	10	52	no
090059	428	Unscheduled kill	,8226	,0485	11	51	no
090045	429	Found death on study	,8065	,0502	12	50	no
090050	452	Unscheduled kill	,7903	,0517	13	49	no
090048	458	Scheduled kill			13	48	no
090018	467	Found death on study	,7739	,0532	14	47	no
090007	478	Unscheduled kill	,7574	,0545	15	46	no
090049	479	Unscheduled kill	,7409	,0558	16	45	no
090053	498	Unscheduled kill	,7245	,0569	17	44	no
090043	499	Unscheduled kill			18	43	no
090052	499	Unscheduled kill	,6915	,0589	19	42	no
090023	505	Unscheduled kill	,6751	,0598	20	41	no
090055	508	Unscheduled kill	,6586	,0605	21	40	no
090003	515	Unscheduled kill			22	39	no
090035	515	Found death on study	,6257	,0618	23	38	no
090024	518	Found death on study	,6092	,0623	24	37	no
090026	523	Found death on study	,5927	,0628	25	36	no
090015	525	Found death on study			26	35	no
090029	525	Found death on study			27	34	no
090057	525	Unscheduled kill	,5433	,0637	28	33	no
090002	546	Scheduled kill			28	32	no
090005	546	Scheduled kill			28	31	no
090040	546	Scheduled kill			28	30	no
090054	546	Scheduled kill			28	29	no
090060	546	Scheduled kill			28	28	no
090006	547	Scheduled kill			28	27	no
090008	547	Scheduled kill			28	26	no
090011	547	Scheduled kill			28	25	no
090012	547	Scheduled kill			28	24	no
090013	547	Scheduled kill			28	23	no
090016	547	Scheduled kill			28	22	no
090017	547	Scheduled kill			28	21	no
090019	547	Scheduled kill			28	20	no
090021	547	Scheduled kill			28	19	no
090022	547	Scheduled kill			28	18	no
090025	548	Scheduled kill			28	17	no
090027	548	Scheduled kill			28	16	no
090028	548	Scheduled kill			28	15	no
090030	548	Scheduled kill			28	14	no
090031	548	Scheduled kill			28	13	no
090032	548	Scheduled kill			28	12	no
090034	548	Scheduled kill			28	11	no
090036	548	Scheduled kill			28	10	no
090037	548	Scheduled kill			28	9	no
090038	549	Scheduled kill			28	8	no
090039	549	Scheduled kill			28	7	no
090041	549	Scheduled kill			28	6	no
090042	549	Scheduled kill			28	5	no
090046	549	Scheduled kill			28	4	no
090051	549	Scheduled kill			28	3	no
090056	549	Scheduled kill			28	2	no
090061	549	Scheduled kill			28	1	no
090062	549	Scheduled kill			28	0	no

Number of Cases: 62 Censored: 34 (54,84%) Events: 28

Appendix A1 (continued): Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = Lower CTP1

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumor
100054	51	Unscheduled kill	,9839	,0160	1	61	no
100028	65	Found death on study	,9677	,0224	2	60	no
100038	177	Unscheduled kill	,9516	,0273	3	59	no
100053	219	Unscheduled kill	,9355	,0312	4	58	no
100007	249	Unscheduled kill	,9194	,0346	5	57	no
100039	269	Unscheduled kill	,9032	,0375	6	56	no
100033	378	Unscheduled kill	,8871	,0402	7	55	no
100018	400	Unscheduled kill	,8710	,0426	8	54	no
100034	415	Unscheduled kill	,8548	,0447	9	53	no
100044	443	Found death on study			10	52	no
100046	443	Unscheduled kill	,8226	,0485	11	51	no
100050	445	Unscheduled kill	,8065	,0502	12	50	no
100012	455	Unscheduled kill	,7903	,0517	13	49	no
100016	478	Unscheduled kill	,7742	,0531	14	48	no
100023	487	Unscheduled kill	,7581	,0544	15	47	no
100009	491	Unscheduled kill	,7419	,0556	16	46	no
100010	501	Unscheduled kill	,7258	,0567	17	45	no
100022	514	Found death on study	,7097	,0576	18	44	no
100008	525	Unscheduled kill	,6935	,0585	19	43	no
100021	527	Unscheduled kill	,6774	,0594	20	42	no
100003	532	Found death on study	,6613	,0601	21	41	no
100030	535	Found death on study	,6452	,0608	22	40	no
100031	541	Unscheduled kill	,6290	,0613	23	39	no
100002	542	Unscheduled kill	,6129	,0619	24	38	no
100041	546	Found death on study	,5968	,0623	25	37	no
100005	546	Scheduled kill			25	36	no
100017	546	Scheduled kill			25	35	no
100051	546	Scheduled kill			25	34	no
100052	546	Scheduled kill			25	33	no
100001	547	Scheduled kill			25	32	no
100004	547	Scheduled kill			25	31	no
100006	547	Scheduled kill			25	30	no
100011	547	Scheduled kill			25	29	no
100013	547	Scheduled kill			25	28	no
100014	547	Scheduled kill			25	27	no
100015	547	Scheduled kill			25	26	no
100019	547	Scheduled kill			25	25	no
100020	547	Scheduled kill			25	24	no
100024	547	Scheduled kill			25	23	no
100025	548	Scheduled kill			25	22	no
100026	548	Scheduled kill			25	21	no
100027	548	Scheduled kill			25	20	no
100029	548	Scheduled kill			25	19	no
100032	548	Scheduled kill			25	18	no
100035	548	Scheduled kill			25	17	no
100036	548	Scheduled kill			25	16	no
100037	548	Scheduled kill			25	15	no
100040	548	Scheduled kill			25	14	no
100042	548	Scheduled kill			25	13	no
100043	549	Scheduled kill			25	12	no
100045	549	Scheduled kill			25	11	no
100047	549	Scheduled kill			25	10	no
100048	549	Scheduled kill			25	9	no
100049	549	Scheduled kill			25	8	no
100055	549	Scheduled kill			25	7	no
100056	549	Scheduled kill			25	6	no
100057	549	Scheduled kill			25	5	no
100058	549	Scheduled kill			25	4	no
100059	549	Scheduled kill			25	3	no
100060	549	Scheduled kill			25	2	no
100061	549	Scheduled kill			25	1	no
100062	549	Scheduled kill			25	0	no

Number of Cases: 62 Censored: 37 (59,68%) Events: 25

Appendix A1 (continued): Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = Lowest CTP2

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumor
110004	165	Unscheduled kill	,9839	,0160	1	61	no
110029	224	Found death on study	,9677	,0224	2	60	no
110033	282	Unscheduled kill	,9516	,0273	3	59	no
110018	296	Unscheduled kill	,9355	,0312	4	58	no
110020	329	Unscheduled kill	,9194	,0346	5	57	no
110014	373	Found death on study	,9032	,0375	6	56	no
110042	427	Found death on study			7	55	no
110059	427	Unscheduled kill	,8710	,0426	8	54	no
110011	443	Unscheduled kill	,8548	,0447	9	53	no
110055	445	Unscheduled kill	,8387	,0467	10	52	no
110053	450	Unscheduled kill	,8226	,0485	11	51	no
110002	451	Unscheduled kill	,8065	,0502	12	50	no
110044	459	Found death on study	,7903	,0517	13	49	no
110037	462	Unscheduled kill	,7742	,0531	14	48	no
110027	473	Unscheduled kill	,7581	,0544	15	47	no
110040	492	Unscheduled kill	,7419	,0556	16	46	no
110007	497	Unscheduled kill	,7258	,0567	17	45	no
110009	514	Unscheduled kill	,7097	,0576	18	44	no
110057	518	Unscheduled kill	,6935	,0585	19	43	no
110001	526	Unscheduled kill	,6774	,0594	20	42	no
110043	527	Unscheduled kill			21	41	no
110047	527	Unscheduled kill	,6452	,0608	22	40	no
110060	529	Unscheduled kill	,6290	,0613	23	39	no
110062	530	Found death on study	,6129	,0619	24	38	no
110056	541	Found death on study	,5968	,0623	25	37	no
110003	546	Scheduled kill			25	36	no
110016	546	Scheduled kill			25	35	no
110032	546	Scheduled kill			25	34	no
110036	546	Scheduled kill			25	33	yes
110054	546	Scheduled kill			25	32	no
110005	547	Scheduled kill			25	31	no
110006	547	Scheduled kill			25	30	no
110008	547	Scheduled kill			25	29	no
110010	547	Scheduled kill			25	28	no
110012	547	Scheduled kill			25	27	no
110013	547	Scheduled kill			25	26	no
110015	547	Scheduled kill			25	25	no
110017	547	Scheduled kill			25	24	no
110019	547	Scheduled kill			25	23	no
110021	547	Scheduled kill			25	22	no
110022	548	Scheduled kill			25	21	no
110023	548	Scheduled kill			25	20	no
110024	548	Scheduled kill			25	19	no
110025	548	Scheduled kill			25	18	no
110026	548	Scheduled kill			25	17	no
110028	548	Scheduled kill			25	16	no
110030	548	Scheduled kill			25	15	no
110031	548	Scheduled kill			25	14	no
110034	548	Scheduled kill			25	13	no
110035	548	Scheduled kill			25	12	no
110038	549	Scheduled kill			25	11	no
110039	549	Scheduled kill			25	10	no
110041	549	Scheduled kill			25	9	no
110045	549	Scheduled kill			25	8	no
110046	549	Scheduled kill			25	7	no
110048	549	Scheduled kill			25	6	no
110049	549	Scheduled kill			25	5	no
110050	549	Scheduled kill			25	4	no
110051	549	Scheduled kill			25	3	no
110052	549	Scheduled kill			25	2	no
110058	549	Scheduled kill			25	1	no
110061	549	Scheduled kill			25	0	no

Number of Cases: 62 Censored: 37 (59,68%) Events: 25

Appendix A1 (continued): Survival Analysis

Survival Analysis for DEATHDAY Days to Death

Factor GROUP = Lower CTP2

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining	Microsc. Tumor
120029	120	Unscheduled kill	,9839	,0160	1	61	no
120010	126	Found death on study	,9677	,0224	2	60	no
120048	228	Unscheduled kill			3	59	no
120061	228	Unscheduled kill	,9355	,0312	4	58	no
120001	245	Unscheduled kill	,9194	,0346	5	57	no
120021	255	Unscheduled kill	,9032	,0375	6	56	no
120009	261	Found death on study	,8871	,0402	7	55	no
120004	262	Unscheduled kill	,8710	,0426	8	54	no
120047	290	Unscheduled kill	,8548	,0447	9	53	no
120058	312	Unscheduled kill	,8387	,0467	10	52	no
120037	381	Unscheduled kill	,8226	,0485	11	51	no
120036	385	Unscheduled kill	,8065	,0502	12	50	no
120059	408	Unscheduled kill	,7903	,0517	13	49	no
120013	428	Found death on study	,7742	,0531	14	48	no
120051	440	Found death on study	,7581	,0544	15	47	no
120053	441	Unscheduled kill	,7419	,0556	16	46	yes
120023	466	Unscheduled kill			17	45	no
120062	466	Found death on study	,7097	,0576	18	44	no
120056	469	Unscheduled kill	,6935	,0585	19	43	no
120060	471	Unscheduled kill	,6774	,0594	20	42	no
120045	483	Unscheduled kill	,6613	,0601	21	41	no
120006	490	Unscheduled kill	,6452	,0608	22	40	no
120026	494	Unscheduled kill	,6290	,0613	23	39	no
120040	497	Unscheduled kill	,6129	,0619	24	38	yes
120055	501	Unscheduled kill	,5968	,0623	25	37	no
120052	502	Unscheduled kill	,5806	,0627	26	36	no
120050	504	Found death on study	,5645	,0630	27	35	yes
120041	524	Found death on study	,5484	,0632	28	34	no
120043	535	Unscheduled kill	,5323	,0634	29	33	no
120039	538	Found death on study	,5161	,0635	30	32	no
120057	544	Found death on study	,5000	,0635	31	31	no
120002	546	Scheduled kill			31	30	no
120003	546	Scheduled kill			31	29	no
120005	546	Scheduled kill			31	28	no
120018	546	Scheduled kill			31	27	no
120022	546	Scheduled kill			31	26	no
120007	547	Scheduled kill			31	25	no
120008	547	Scheduled kill			31	24	no
120011	547	Scheduled kill			31	23	no
120012	547	Scheduled kill			31	22	no
120014	547	Scheduled kill			31	21	no
120015	547	Scheduled kill			31	20	no
120016	547	Scheduled kill			31	19	no
120017	547	Scheduled kill			31	18	no
120019	547	Scheduled kill			31	17	no
120020	547	Scheduled kill			31	16	no
120024	548	Scheduled kill			31	15	no
120025	548	Scheduled kill			31	14	no
120027	548	Scheduled kill			31	13	no
120028	548	Scheduled kill			31	12	no
120030	548	Scheduled kill			31	11	no
120031	548	Scheduled kill			31	10	no
120032	548	Scheduled kill			31	9	no
120033	548	Scheduled kill			31	8	no
120034	548	Scheduled kill			31	7	no
120035	549	Scheduled kill			31	6	no
120038	549	Scheduled kill			31	5	no
120042	549	Scheduled kill			31	4	no
120044	549	Scheduled kill			31	3	no
120046	549	Scheduled kill			31	2	no
120049	549	Scheduled kill			31	1	no
120054	549	Scheduled kill			31	0	no

Number of Cases: 62 Censored: 31 (50,00%) Events: 31

Appendix A2: Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
010008	11	no			0	61
010052	45	no			0	60
010038	204	no			0	59
010023	254	no			0	58
010018	291	no			0	57
010031	364	no			0	56
010044	365	no			0	55
010015	401	no			0	54
010037	435	no			0	53
010005	439	no			0	52
010062	449	no			0	51
010047	466	no			0	50
010009	472	no			0	49
010029	479	no			0	48
010022	483	no			0	47
010016	484	no			0	46
010046	492	no			0	45
010061	503	no			0	44
010032	512	yes	,9773	,0225	1	43
010026	514	no			1	42
010035	515	no			1	41
010059	515	no			1	40
010011	517	no			1	39
010030	532	no			1	38
010024	543	no			1	37
010049	545	no			1	36
010001	546	no			1	35
010002	546	no			1	34
010003	546	no			1	33
010004	547	no			1	32
010006	547	no			1	31
010007	547	no			1	30
010010	547	no			1	29
010012	547	no			1	28
010013	547	no			1	27
010014	547	no			1	26
010017	547	no			1	25
010019	547	no			1	24
010020	548	no			1	23
010021	548	no			1	22
010025	548	no			1	21
010027	548	no			1	20
010028	548	no			1	19
010033	548	no			1	18
010034	548	no			1	17
010036	548	no			1	16
010039	549	no			1	15
010040	549	no			1	14
010041	549	no			1	13
010042	549	no			1	12
010043	549	no			1	11
010045	549	no			1	10
010048	549	no			1	9
010050	549	no			1	8
010051	549	no			1	7
010053	549	no			1	6
010054	549	no			1	5
010055	550	no			1	4
010056	550	no			1	3
010057	550	no			1	2
010058	550	no			1	1
010060	550	no			1	0

Number of Cases: 62 Censored: 61 (98,39%) Events: 1

	Survival Time	Standard Error	95% Confidence Interval	
Mean:	549	1	(547;	551)
(Limited to	550)			
Median:	.	.	(.	.)

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
020050	184	yes	,9839	,0160	1	61
020021	198	yes			2	60
020045	198	yes			3	59
020054	198	yes			4	58
020056	198	yes	,9194	,0346	5	57
020001	205	yes			6	56
020008	205	yes			7	55
020027	205	yes			8	54
020028	205	yes			9	53
020029	205	yes			10	52
020037	205	yes			11	51
020061	205	yes	,8065	,0502	12	50
020057	219	yes	,7903	,0517	13	49
020020	254	yes			14	48
020031	254	yes			15	47
020053	254	yes	,7419	,0556	16	46
020012	261	yes			17	45
020062	261	yes	,7097	,0576	18	44
020014	261	no			18	43
020033	268	yes	,6932	,0586	19	42
020002	289	yes			20	41
020010	289	yes	,6602	,0603	21	40
020004	296	yes			22	39
020006	296	yes			23	38
020013	296	yes			24	37
020036	296	yes	,5941	,0627	25	36
020049	303	yes	,5776	,0631	26	35
020043	310	yes	,5611	,0634	27	34
020022	317	yes			28	33
020025	317	yes			29	32
020051	317	yes	,5116	,0639	30	31
020059	322	no			30	30
020007	324	yes			31	29
020015	324	yes			32	28
020041	324	yes			33	27
020052	324	yes	,4434	,0638	34	26
020005	331	yes			35	25
020024	331	yes	,4093	,0633	36	24
020038	345	yes	,3922	,0629	37	23
020017	359	yes	,3752	,0625	38	22
020040	366	yes	,3581	,0619	39	21
020047	373	yes			40	20
020060	373	yes	,3240	,0605	41	19
020011	380	yes			42	18
020030	380	yes	,2899	,0588	43	17
020035	387	yes	,2729	,0577	44	16
020058	401	yes	,2558	,0566	45	15
020046	408	yes	,2388	,0553	46	14
020055	415	no			46	13
020019	443	yes	,2204	,0540	47	12
020039	450	yes			48	11
020048	450	yes	,1837	,0509	49	10
020034	465	no			49	9
020042	499	yes	,1633	,0492	50	8
020018	520	yes	,1428	,0471	51	7
020032	527	yes	,1224	,0445	52	6
020026	541	yes	,1020	,0415	53	5
020003	546	no			53	4
020009	546	no			53	3
020016	547	no			53	2
020023	548	no			53	1
020044	549	no			53	0

Number of Cases: 62 Censored: 9 (14,52%) Events: 53

	Survival Time	Standard Error	95% Confidence Interval	
Mean:	343	15	(315;	372)
(Limited to	549)			
Median:	324	8	(309;	339)

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
030039	248	no			0	61
030050	312	no			0	60
030025	317	no			0	59
030033	319	no			0	58
030053	339	no			0	57
030003	345	no			0	56
030046	373	no			0	55
030045	381	no			0	54
030035	394	yes	,9815	,0183	1	53
030049	398	no			1	52
030056	409	no			1	51
030009	414	no			1	50
030047	414	no			1	49
030057	414	no			1	48
030005	415	no			1	47
030001	416	no			1	46
030004	416	no			1	45
030061	424	no			1	44
030013	438	no			1	43
030021	440	no			1	42
030034	441	no			1	41
030007	442	no			1	40
030062	452	no			1	39
030020	461	no			1	38
030024	470	no			1	37
030026	484	no			1	36
030017	491	no			1	35
030040	496	no			1	34
030060	497	no			1	33
030055	505	no			1	32
030030	528	no			1	31
030051	528	no			1	30
030002	534	no			1	29
030037	535	no			1	28
030006	546	no			1	27
030008	546	no			1	26
030010	546	no			1	25
030011	547	no			1	24
030012	547	no			1	23
030014	547	no			1	22
030015	547	no			1	21
030016	547	no			1	20
030018	547	no			1	19
030019	548	no			1	18
030022	548	no			1	17
030023	548	no			1	16
030027	548	no			1	15
030028	548	no			1	14
030029	548	no			1	13
030031	548	no			1	12
030032	549	no			1	11
030036	549	no			1	10
030038	549	no			1	9
030041	549	no			1	8
030042	549	no			1	7
030043	549	no			1	6
030044	549	no			1	5
030048	549	no			1	4
030052	550	no			1	3
030054	550	no			1	2
030058	550	no			1	1
030059	550	no			1	0

Number of Cases: 62 Censored: 61 (98,39%) Events: 1

	Survival Time	Standard Error	95% Confidence Interval
Mean:	547	3	(542, 553)
(Limited to	550)		
Median:	.	.	(. , .)

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
040040	172	no			0	61
040032	225	no			0	60
040017	228	no			0	59
040044	232	no			0	58
040060	234	no			0	57
040046	240	yes	,9825	,0174	1	56
040058	261	no			1	55
040036	269	no			1	54
040052	282	yes	,9643	,0248	2	53
040037	317	no			2	52
040008	340	no			2	51
040047	346	no			2	50
040039	395	no			2	49
040050	395	no			2	48
040020	396	no			2	47
040016	400	no			2	46
040028	406	no			2	45
040006	420	no			2	44
040023	421	no			2	43
040043	422	no			2	42
040010	453	no			2	41
040014	457	no			2	40
040059	463	no			2	39
040009	469	no			2	38
040049	473	no			2	37
040027	487	no			2	36
040003	490	no			2	35
040022	497	no			2	34
040041	500	no			2	33
040007	512	no			2	32
040025	519	no			2	31
040057	520	no			2	30
040021	535	no			2	29
040054	538	no			2	28
040048	541	no			2	27
040031	545	no			2	26
040001	546	no			2	25
040002	546	no			2	24
040004	546	no			2	23
040005	547	no			2	22
040011	547	no			2	21
040012	547	no			2	20
040013	547	no			2	19
040015	547	no			2	18
040018	547	no			2	17
040019	548	no			2	16
040024	548	no			2	15
040026	548	no			2	14
040029	548	no			2	13
040030	548	no			2	12
040033	548	no			2	11
040034	549	no			2	10
040035	549	no			2	9
040038	549	no			2	8
040042	549	no			2	7
040045	549	no			2	6
040051	549	no			2	5
040053	549	no			2	4
040055	550	no			2	3
040056	550	no			2	2
040061	550	no			2	1
040062	550	no			2	0

Number of Cases: 62 Censored: 60 (96,77%) Events: 2

	Survival Time	Standard Error	95% Confidence Interval	
Mean:	540	7	(526;	554)
(Limited to	550)			
Median:			(	)

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor .

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
050061	212	yes	,9839	,0160	1	61
050040	214	no			1	60
050006	219	no			1	59
050003	241	no			1	58
050031	247	no			1	57
050022	256	no			1	56
050056	256	no			1	55
050033	261	no			1	54
050060	305	no			1	53
050029	312	no			1	52
050044	340	no			1	51
050043	344	no			1	50
050011	346	no			1	49
050012	347	no			1	48
050059	368	no			1	47
050007	384	no			1	46
050026	385	no			1	45
050009	388	no			1	44
050037	389	no			1	43
050038	396	no			1	42
050054	402	no			1	41
050017	415	yes	,9599	,0284	2	40
050036	415	no			2	39
050002	416	no			2	38
050004	417	no			2	37
050013	421	no			2	36
050027	448	no			2	35
050032	450	no			2	34
050024	452	no			2	33
050041	464	no			2	32
050014	467	no			2	31
050023	469	no			2	30
050035	481	no			2	29
050049	484	no			2	28
050001	490	no			2	27
050010	494	no			2	26
050052	498	no			2	25
050051	520	yes	,9215	,0464	3	24
050055	525	no			3	23
050020	527	yes	,8814	,0592	4	22
050042	529	no			4	21
050046	539	no			4	20
050039	543	no			4	19
050005	546	no			4	18
050008	546	no			4	17
050015	546	no			4	16
050019	546	no			4	15
050016	547	no			4	14
050018	547	no			4	13
050021	547	no			4	12
050025	547	no			4	11
050028	547	no			4	10
050030	548	no			4	9
050034	548	no			4	8
050045	548	no			4	7
050047	548	no			4	6
050048	548	no			4	5
050050	549	no			4	4
050053	549	no			4	3
050057	549	no			4	2
050058	550	no			4	1
050062	550	no			4	0

Number of Cases: 62 Censored: 58 (93,55%) Events: 4

	Survival Time	Standard Error	95% Confidence Interval	
Mean:	539	6	(527,	552)
(Limited to	550)			
Median:				)

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
060058	16	no			0	61
060020	39	no			0	60
060004	59	no			0	59
060062	121	yes	,9831	,0168	1	58
060017	191	yes	,9661	,0236	2	57
060021	205	yes	,9492	,0286	3	56
060023	210	no			3	55
060032	229	no			3	54
060005	247	no			3	53
060059	247	no			3	52
060018	255	no			3	51
060025	255	no			3	50
060036	261	yes			4	49
060060	261	yes	,9112	,0380	5	48
060014	289	yes	,8922	,0417	6	47
060015	297	no			6	46
060013	310	yes	,8728	,0451	7	45
060061	317	yes	,8534	,0481	8	44
060052	331	yes	,8340	,0507	9	43
060003	336	no			9	42
060041	358	no			9	41
060030	371	no			9	40
060029	379	no			9	39
060037	380	yes	,8126	,0538	10	38
060035	387	yes	,7912	,0564	11	37
060051	387	no			11	36
060049	388	no			11	35
060044	389	no			11	34
060053	406	no			11	33
060002	412	no			11	32
060012	417	no			11	31
060045	429	yes	,7657	,0601	12	30
060050	443	yes	,7402	,0633	13	29
060048	468	no			13	28
060047	475	no			13	27
060016	478	yes	,7128	,0666	14	26
060010	482	no			14	25
060039	485	yes	,6843	,0698	15	24
060057	490	no			15	23
060009	492	yes	,6545	,0728	16	22
060034	502	no			16	21
060054	511	no			16	20
060033	514	no			16	19
060043	536	no			16	18
060006	541	yes	,6182	,0773	17	17
060027	543	no			17	16
060001	546	no			17	15
060007	546	no			17	14
060008	547	no			17	13
060011	547	no			17	12
060019	547	no			17	11
060022	548	no			17	10
060024	548	no			17	9
060026	548	no			17	8
060028	548	no			17	7
060031	548	no			17	6
060038	548	no			17	5
060040	549	no			17	4
060042	549	no			17	3
060046	550	no			17	2
060055	550	no			17	1
060056	550	no			17	0

Number of Cases: 62 Censored: 45 (72,58%) Events: 17

	Survival Time	Standard Error	95% Confidence Interval	
Mean:	483	,15	(452;	513)
(Limited to	550)			
Median:	,			

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
070035	10	no			0	61
070008	157	no			0	60
070021	163	yes	,9833	,0165	1	59
070052	170	yes	,9667	,0232	2	58
070012	205	yes			3	57
070050	205	yes	,9333	,0322	4	56
070058	211	no			4	55
070051	212	yes	,9164	,0358	5	54
070029	213	no			5	53
070044	214	no			5	52
070056	226	yes	,8987	,0392	6	51
070039	231	no			6	50
070002	261	yes			7	49
070003	261	yes			8	48
070028	261	yes	,8448	,0476	9	47
070001	261	no			9	46
070038	266	no			9	45
070004	268	yes	,8260	,0502	10	44
070040	268	no			10	43
070036	281	no			10	42
070032	282	yes	,8064	,0527	11	41
070042	289	yes	,7867	,0549	12	40
070060	297	no			12	39
070007	299	no			12	38
070016	305	no			12	37
070046	310	yes	,7654	,0574	13	36
070061	317	yes			14	35
070062	317	yes	,7229	,0616	15	34
070020	324	yes			16	33
070027	324	yes			17	32
070034	324	yes	,6591	,0663	18	31
070023	331	yes			19	30
070041	331	yes	,6166	,0685	20	29
070045	339	no			20	28
070013	347	no			20	27
070011	353	yes	,5938	,0696	21	26
070053	359	yes	,5709	,0706	22	25
070059	364	yes	,5481	,0714	23	24
070026	366	yes	,5253	,0720	24	23
070025	373	yes	,5024	,0724	25	22
070005	380	yes	,4796	,0726	26	21
070019	380	no			26	20
070006	387	yes			27	19
070022	387	yes			28	18
070057	387	yes	,4076	,0726	29	17
070055	401	yes	,3837	,0722	30	16
070014	408	yes	,3597	,0716	31	15
070037	409	no			31	14
070017	413	no			31	13
070015	424	no			31	12
070024	436	yes	,3297	,0716	32	11
070033	443	yes	,2997	,0711	33	10
070047	450	no			33	9
070054	452	no			33	8
070010	456	no			33	7
070048	457	yes	,2569	,0727	34	6
070049	472	no			34	5
070031	483	no			34	4
070009	506	yes	,1927	,0779	35	3
070043	508	no			35	2
070030	538	no			35	1
070018	548	no			35	0

Number of Cases: 62 Censored: 27 (43,55%) Events: 35

	Survival Time	Standard Error	95% Confidence Interval	
Mean:	506	16	(355,	416)
(Limited to	548)			
Median:	380	12	(356,	[illegible]

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
080037	72	yes	,9836	,0163	1	60
080002	72	no			1	59
080014	114	no			1	58
080001	119	no			1	57
080023	142	yes	,9664	,0234	2	56
080012	156	yes	,9491	,0286	3	55
080051	171	no			3	54
080062	171	no			3	53
080044	177	yes			4	52
080057	177	yes	,9133	,0371	5	51
080027	184	yes			6	50
080048	184	yes			7	49
080056	184	yes	,8596	,0461	8	48
080022	191	yes			9	47
080024	191	yes			10	46
080034	191	yes	,8056	,0526	11	45
080033	192	no			11	44
080049	193	no			11	43
080026	198	yes			12	42
080028	198	yes			13	41
080046	198	yes	,7496	,0581	14	40
080015	205	yes			15	39
080032	205	yes			16	38
080035	205	yes	,6934	,0622	17	37
080008	212	yes			18	36
080016	212	yes			19	35
080031	212	yes			20	34
080061	212	yes	,6184	,0658	21	33
080013	219	yes			22	32
080059	219	yes	,5810	,0669	23	31
080004	220	no			23	30
080011	224	no			23	29
080017	226	yes			24	28
080045	226	yes			25	27
080058	226	yes			26	26
080060	226	yes	,5008	,0686	27	25
080018	227	no			27	24
080038	233	yes			28	23
080055	233	yes	,4591	,0690	29	22
080052	238	no			29	21
080036	239	no			29	20
080021	240	yes			30	19
080047	240	yes	,4132	,0693	31	18
080003	243	no			31	17
080029	247	yes	,3689	,0694	32	16
080054	260	no			32	15
080009	268	yes			33	14
080040	268	yes			34	13
080041	268	yes			35	12
080043	268	yes	,2852	,0675	36	11
080010	269	no			36	10
080019	269	no			36	9
080025	269	no			36	8
080050	269	no			36	7
080053	269	no			36	6
080005	274	no			36	5
080007	274	no			36	4
080020	274	no			36	3
080030	274	no			36	2
080039	274	no			36	1
080042	274	no			36	0

Number of Cases: 61 Censored: 25 (41,94%) Events: 36

	Survival Time	Standard Error	95% Confidence Interval
Mean:	230	6	(219; 241)
(Limited to	274)		
Median:	233	9	(216; 250)

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
090020	7	no			0	61
090044	38	no			0	60
090009	120	no			0	59
090033	126	no			0	58
090014	135	no			0	57
090001	151	no			0	56
090004	179	no			0	55
090047	245	no			0	54
090058	295	no			0	53
090010	370	no			0	52
090059	428	no			0	51
090045	429	no			0	50
090050	452	no			0	49
090048	458	no			0	48
090018	467	no			0	47
090007	478	no			0	46
090049	479	no			0	45
090053	498	no			0	44
090043	499	no			0	43
090052	499	no			0	42
090023	505	no			0	41
090055	508	no			0	40
090003	515	no			0	39
090035	515	no			0	38
090024	518	no			0	37
090026	523	no			0	36
090015	525	no			0	35
090029	525	no			0	34
090057	525	no			0	33
090002	546	no			0	32
090005	546	no			0	31
090040	546	no			0	30
090054	546	no			0	29
090060	546	no			0	28
090006	547	no			0	27
090008	547	no			0	26
090011	547	no			0	25
090012	547	no			0	24
090013	547	no			0	23
090016	547	no			0	22
090017	547	no			0	21
090019	547	no			0	20
090021	547	no			0	19
090022	547	no			0	18
090025	548	no			0	17
090027	548	no			0	16
090028	548	no			0	15
090030	548	no			0	14
090031	548	no			0	13
090032	548	no			0	12
090034	548	no			0	11
090036	548	no			0	10
090037	548	no			0	9
090038	549	no			0	8
090039	549	no			0	7
090041	549	no			0	6
090042	549	no			0	5
090046	549	no			0	4
090051	549	no			0	3
090056	549	no			0	2
090061	549	no			0	1
090062	549	no			0	0

>Warning # 20077. Command name: KM
>Survival estimates cannot be computed since all observations are censored.

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
100054	51	no			0	61
100028	65	no			0	60
100038	177	no			0	59
100053	219	no			0	58
100007	249	no			0	57
100039	269	no			0	56
100033	378	no			0	55
100018	400	no			0	54
100034	415	no			0	53
100044	443	no			0	52
100046	443	no			0	51
100050	445	no			0	50
100012	455	no			0	49
100016	478	no			0	48
100023	487	no			0	47
100009	491	no			0	46
100010	501	no			0	45
100022	514	no			0	44
100008	525	no			0	43
100021	527	no			0	42
100003	532	no			0	41
100030	535	no			0	40
100031	541	no			0	39
100002	542	no			0	38
100005	546	no			0	37
100017	546	no			0	36
100041	546	no			0	35
100051	546	no			0	34
100052	546	no			0	33
100001	547	no			0	32
100004	547	no			0	31
100006	547	no			0	30
100011	547	no			0	29
100013	547	no			0	28
100014	547	no			0	27
100015	547	no			0	26
100019	547	no			0	25
100020	547	no			0	24
100024	547	no			0	23
100025	548	no			0	22
100026	548	no			0	21
100027	548	no			0	20
100029	548	no			0	19
100032	548	no			0	18
100035	548	no			0	17
100036	548	no			0	16
100037	548	no			0	15
100040	548	no			0	14
100042	548	no			0	13
100043	549	no			0	12
100045	549	no			0	11
100047	549	no			0	10
100048	549	no			0	9
100049	549	no			0	8
100055	549	no			0	7
100056	549	no			0	6
100057	549	no			0	5
100058	549	no			0	4
100059	549	no			0	3
100060	549	no			0	2
100061	549	no			0	1
100062	549	no			0	0

>Warning # 20077. Command name: KM
>Survival estimates cannot be computed since all observations are censored.

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
110004	165	no			0	61
110029	224	no			0	60
110033	282	no			0	59
110018	296	no			0	58
110020	329	no			0	57
110036	345	yes	,9825	,0174	1	56
110014	373	no			1	55
110037	394	yes	,9646	,0246	2	54
110042	427	no			2	53
110059	427	no			2	52
110011	443	no			2	51
110055	445	no			2	50
110053	450	no			2	49
110002	451	no			2	48
110044	459	no			2	47
110027	473	no			2	46
110040	492	no			2	45
110007	497	no			2	44
110009	514	no			2	43
110057	518	no			2	42
110001	526	no			2	41
110043	527	no			2	40
110047	527	no			2	39
110060	529	no			2	38
110062	530	no			2	37
110056	541	no			2	36
110003	546	no			2	35
110016	546	no			2	34
110032	546	no			2	33
110054	546	no			2	32
110005	547	no			2	31
110006	547	no			2	30
110008	547	no			2	29
110010	547	no			2	28
110012	547	no			2	27
110013	547	no			2	26
110015	547	no			2	25
110017	547	no			2	24
110019	547	no			2	23
110021	547	no			2	22
110022	548	no			2	21
110023	548	no			2	20
110024	548	no			2	19
110025	548	no			2	18
110026	548	no			2	17
110028	548	no			2	16
110030	548	no			2	15
110031	548	no			2	14
110034	548	no			2	13
110035	548	no			2	12
110038	549	no			2	11
110039	549	no			2	10
110041	549	no			2	9
110045	549	no			2	8
110046	549	no			2	7
110048	549	no			2	6
110049	549	no			2	5
110050	549	no			2	4
110051	549	no			2	3
110052	549	no			2	2
110058	549	no			2	1
110061	549	no			2	0

Number of Cases: 62 Censored: 60 (96,77%) Events: 2

	Survival Time	Standard Error	95% Confidence Interval	
Mean:	543	4	(534,	551)
(Limited to	549)			
Median:	.		(.	.)

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

ID	Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
120040	114	yes	,9839	,0160	1	61
120029	120	no			1	60
120010	126	no			1	59
120048	228	no			1	58
120061	228	no			1	57
120001	245	no			1	56
120021	255	no			1	55
120009	261	no			1	54
120004	262	no			1	53
120053	268	yes	,9653	,0242	2	52
120015	289	yes	,9467	,0300	3	51
120047	290	no			3	50
120058	312	no			3	49
120057	359	yes	,9274	,0351	4	48
120012	366	yes	,9081	,0393	5	47
120037	381	no			5	46
120036	385	no			5	45
120059	408	no			5	44
120013	428	no			5	43
120051	440	no			5	42
120050	450	yes	,8865	,0439	6	41
120023	466	no			6	40
120062	466	no			6	39
120056	469	no			6	38
120060	471	no			6	37
120045	483	no			6	36
120006	490	no			6	35
120026	494	no			6	34
120055	501	no			6	33
120052	502	no			6	32
120041	524	no			6	31
120043	535	no			6	30
120039	538	no			6	29
120002	546	no			6	28
120003	546	no			6	27
120005	546	no			6	26
120018	546	no			6	25
120022	546	no			6	24
120007	547	no			6	23
120008	547	no			6	22
120011	547	no			6	21
120014	547	no			6	20
120016	547	no			6	19
120017	547	no			6	18
120019	547	no			6	17
120020	547	no			6	16
120024	548	no			6	15
120025	548	no			6	14
120027	548	no			6	13
120028	548	no			6	12
120030	548	no			6	11
120031	548	no			6	10
120032	548	no			6	9
120033	548	no			6	8
120034	548	no			6	7
120035	549	no			6	6
120038	549	no			6	5
120042	549	no			6	4
120044	549	no			6	3
120046	549	no			6	2
120049	549	no			6	1
120054	549	no			6	0

Number of Cases: 62 Censored: 56 (90,32%) Events: 6

	Survival Time	Standard Error	95% Confidence Interval	
Mean:	523	11	501,	544)
(Limited to	549)			
Median:				

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

		Total	Number Events	Number Censored	Percent Censored
GROUP	Negat. Cont.	62	1	61	98,39
GROUP	Posit. Cont.	62	53	9	14,52
GROUP	Low CTP1	62	1	61	98,39
GROUP	Medium CTP1	62	2	60	96,77
GROUP	High CTP1	62	4	58	93,55
Overall		310	61	249	80,32

Log Rank Statistic and (Significance)

Factor	1	2	3	4
2	97,81 (,0000)			
3	,01 (,9054)	96,52 (,0000)		
4	,48 (,4863)	83,94 (,0000)	,44 (,5094)	
5	3,12 (,0775)	77,55 (,0000)	2,45 (,1175)	,86 (,3549)

Survival Analysis for TUMORDAY Day of Tumor

		Total	Number Events	Number Censored	Percent Censored
GROUP	Negat. Cont.	62	1	61	98,39
GROUP	Posit. Cont.	62	53	9	14,52
GROUP	Low CTP2	62	17	45	72,58
GROUP	Medium CTP2	62	35	27	43,55
GROUP	High CTP2	61	36	25	40,98
Overall		309	142	167	54,05

Log Rank Statistic and (Significance)

Factor	1	2	6	7
2	97,81 (,0000)			
6	21,44 (,0000)	37,41 (,0000)		
7	68,61 (,0000)	3,63 (,0567)	18,88 (,0000)	
8	65,01 (,0000)	18,81 (,0000)	45,30 (,0000)	33,71 (,0000)

Appendix A2 (continued): Survival Analysis with Macroscopic Onset of Tumours

Survival Analysis for TUMORDAY Day of Tumor

		Total	Number Events	Number Censored	Percent Censored
GROUP	Negat. Cont. 2	62	0	62	100,00
GROUP	Lower CTP1	62	0	62	100,00
GROUP	Lowest CTP2	62	2	60	96,77
GROUP	Lower CTP2	62	6	56	90,32
Overall		248	8	240	96,77

Log Rank Statistic and (Significance)

Factor	9	10	11
10	(,)		
11	1,88 (,1709)	1,98 (,1591)	
12	6,39 (,0115)	6,61 (,0101)	2,58 (,1082)

. is used where test statistics cannot be computed

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