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INIT 11/17/93

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November 15, 1993

Document Processing Center (7407)
(Attention: Section 8(e) Coordinator)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M St., SW
Washington, DC 20460



REC'D
OFFICE OF POLLUTION
PREVENTION AND TOXICS
03 NOV 17 AM 7:38

Dear Section 8(e) Coordinator:

Subject: TSCA 8(e) Notice - CGI 403: Supplemental Submission

Ciba-Geigy Corporation (Ciba) claims no information in this letter as Confidential Business Information.

In accordance with EPA's March 16, 1978 policy statement on Section 8(e) reporting under the Toxic Substances Control Act, and EPA's June, 1991 TSCA Section 8(e) Reporting Guide, Ciba wishes to bring to the attention of the Environmental Protection Agency results seen in a subacute toxicity study conducted with CGI 403. CGI 403 is bis(2,6-dimethoxybenzoyl)-2,4,4-trimethylpentylphosphine oxide, having CASRN 145052-34-2.

CGI 403 is a photoinitiator for coatings. It was the subject of PMN P93-0495 submitted by Ciba; the statutory review period has expired.

This study was recently obtained from Ciba's parent company, Ciba-Geigy Limited of Basel, Switzerland. A copy of the study, entitled "28 days subacute, oral toxicity study in rats (gavage)", is enclosed. In this study, rats were dosed daily by oral gavage at levels of 0, 5, 25, 100, and 500 mg/kg for four weeks. The NOEL was 5 mg/kg with the primary effect being cholinesterase inhibition at all other dosages. Liver and adrenal cortex changes were seen at the highest levels. These effects were reversible. These study results confirm the 14-day results previously submitted to EPA on July 16, 1993 (see below).

Four previous TSCA 8(e) notices were submitted for the subject chemical substance: the first on December 30, 1992 for a Guinea Pig Maximization Test; the second on March 4, 1993 for a preliminary assessment of the fourth submission in connection with PMN P93-0495; the third on June 22, 1993 for a dermal sensitization reaction seen in a chemist; and the fourth on July 16, 1993 for a 14-day range finding study in rats (gavage). We have not yet received the Document Control 8(e) Log Number for these submissions.

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11/28/93

357 pgs.

For Data Info see
Public file pgs 45-355

As a result of this new information, Ciba will revise its Material Safety Data Sheet (MSDS) and label as necessary to reflect the new findings and notify relevant workers in accordance with the notification requirements of OSHA's Hazard Communication Standard (29 CFR 1910.1200).

Please call the undersigned if you have any questions about this submittal.

Very truly yours,



Anthony DiBattista

Enclosure

Contains No CBI

28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)

Test No. 924164

TKA 40049 (CGI 403)

FINAL REPORT

93 NOV 17 AM 7:39

REC'D
OFFICE OF POLLUTION
PREVENTION AND TOXICS

Study Director: Dr. rer. nat. R. Gerspach

Testing Facility: CIBA-GEIGY Limited
Short / Long-term Toxicology
4332 Stein / Switzerland

Test Guidelines: OECD 407
84/449/EEC B.7
JAP (EA 700, MHW 1039, MITI 1014)
TSCA 798.6050

Study completed: September 1, 1993

Sponsor: CIBA-GEIGY Limited
Additives Division
4002 Basle / Switzerland

This report contains: 355 pages

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28 DAYS SUBACQUE, ORAL TOXICITY STUDY IN RATS (M/F),
Test No.: 924164
Test Article: TKA 40049

0.1. Proprietary Information

Proprietary information of CIBA-GEIGY Limited.
Not to be disclosed to third parties without previous consent
of CIBA-GEIGY Limited.

0.2. Certification of GLP and Verification of the Report

(Certification of Good Laboratory Practice and Verification of a Complete and Unaltered Copy of the Report by the Sponsor)

The Statement of Compliance with Good Laboratory Practice found on page 4 of this report, and signed by the Study Director is truthful and accurate, and this report as provided by the testing facility is complete and unaltered.

For the Sponsor:

G. K. H. H. H.
.....

date:

Sept 10, 1993

0.3. Statement of Compliance with Good Laboratory Practice

This study has been performed in compliance with Good Laboratory Practice (GLP) in Switzerland, Procedures and Principles, March 1986 (Verfahren und Grundsätze der Guten Laborpraxis (GLP) in der Schweiz), issued by the Swiss Federal Department of the Interior and the Intercantonal Office for the Control of Medicaments. These procedures are in essence consistent with:

- OECD Principles of Good Laboratory Practice (Council Decision 81/30, adopted on May 12, 1981, and the OECD Recommendation 83/95 concerning the 'Mutual Recognition of Compliance with Good Laboratory Practice', adopted on July 26, 1983).
- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 160 (FIFRA); Federal Register, August 17, 1989.
- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 792 (TSCA); Federal Register, August 17, 1989.
- Japan Ministry of Agriculture, Forestry and Fisheries, NohSan, Notification No. 3850, Agricultural Production Bureau, August 10, 1984.

Study Director:

Dr. rer. nat. R. Gerspach

R. Gerspach

.....
date:

September 1, 1993

0.4. Signatures

This report presents the results of the investigations as compiled by the undersigned.

Study Director

Dr. rer. nat. R. Gerspach

..... *R. Gerspach*
date: *September 1, 1993*

Reviewed by

Dr. phil.- nat. H. Fankhauser
Head Longterm Toxicology

..... *H. Fankhauser*
date: *September 2, 1993*

Responsible for
Neurological Investigations

Dr. sc. nat. W. Classen

..... *W. Classen*
date: *September 2, 1993*

Responsible for
Laboratory Investigations

Dr. med. vet. P. Gretener
FVH Clinical Chemistry

..... *P. Gretener*
date: *September 2, 1993*

Responsible for Pathology for

Dr. med. vet. K. Heider (*absent*)
FVH Pathology
Head of Toxicologic Pathology

..... *K. Heider*
date: *September 2, 1993*

Responsible for Neuropathology

G. J. Krinke, MVDr, C.Sc.
FVH Pathology

..... *G. J. Krinke*
date: *September 3, 1993*

Reviewing Pathologist

Dr. med. vet. Ch. Landes,
FTA Pathology

.....*Ch. Landes*.....
date: *September 2, 1993*

Study Pathologist

for

Dr. med. vet. V. Pace, (*absent*)
FVH Pathology

.....*V. Pace*.....
date: *September 2, 1993*

Responsible for Statistics

P. Christen, dipl. stat.

.....*P. Christen*.....
date: *September 7, 1993*

Facility Management

Dr. med. vet. W. Gfeller
FVH Toxicology

.....*W. Gfeller*.....
date: *September 2, 1993*

28 DAYS SUBACUTE, ORAL TOXICITY STUDY IN RATS (GAVAGE)
Test No.: 924164
Test Article: TKA 40049

0.5. Reserved Page for Flagging Statements

0.6. Quality Assurance Statement

I hereby certify that the following Quality Assurance activities were performed :

| QA-Activity | Date performed | Date reported |
|------------------------|----------------|---------------|
| 1) Facility Inspection | 17.09.92 | 30.09.92 |
| 2) Protocol Audit | 08.03.93 | 08.03.93 |
| 3) Facility Inspection | 17.03.93 | 02.04.93 |
| 4) Study Inspection | 17.03.93 | 18.03.93 |
| 5) Study Inspection | 24.03.93 | 24.03.93 |
| 6) Study Inspection | 13.04.93 | 15.04.93 |
| 7) Study Inspection | 13.05.93 | 13.05.93 |
| 8) Data Audit | 03.06.93 | 04.06.93 |
| 9) Data Audit | 14.06.93 | 14.06.93 |
| 10) Final Report Audit | 27.07.93 | 27.07.93 |

Quality Assurance
Inspector :

H. Schneynlin

H. Schneynlin

September 2, 1993

2000

1. INTRODUCTION

Purpose

This toxicity study in rats was conducted in order to determine the oral toxicity (including neurotoxicity) of the test article upon daily administration by gavage for 4 weeks, to estimate a no-effect level of exposure and to determine the degree of reversibility of expected adverse effects at the end of a 4-week recovery period.

Good laboratory practice

This study was carried out in accordance with the Principles of Good Laboratory Practice as set forth in "Verfahren und Grundsätze der Guten Laborpraxis (GLP) in der Schweiz", Swiss Federal Department of the Interior and Intercantonal Office for the Control of Medicaments (IKS), March 1986.

The study was subjected to periodic internal quality assurance evaluation.

Basis for the study

The study was carried out according to the following guidelines:

- OECD Guideline for testing of chemicals, No.407, "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-day Study", adopted May 12, 1981.
- EEC Directive, Official Journal of the European Communities, 19.9.84, 84/449/EEC B.7., Sub-acute Toxicity (oral).
- Requirements of the Japanese Government under the revised Chemical Substance Law (1987) according to the notification of Dec. 9, 1986 by EA (No. 700), MHW (No. 1039) and MITI (No. 1014).
- TSCA, 40 CFR, subpart G: Neurotoxicity; §798.6050, Functional Observational Battery

Sponsor

CIBA-GEIGY Limited
Additives Division
4002 Basle / Switzerland

Testing facility

All in-life testing was performed at the Sisseln facility:

CIBA-GEIGY Limited
Short/Long-term Toxicology
4332 Stein / Switzerland

Histopathological examination was performed at:

CIBA-GEIGY Limited
Short/Long-term Toxicology (Pathology)
4002 Basle / Switzerland

Analytical examinations were performed at:

Analytical Development AD
CIBA-GEIGY Limited
4002 Basle / Switzerland

Personnel and responsible scientists

The following scientists, professionals and supervisory personnel were involved in the conduct of the study:

| | |
|--|--|
| Study director: | Dr. rer. nat. R. Gerspach Longterm Toxicology |
| Technical assistant: | T. Wernli Longterm Toxicology |
| Supervisor: | U. Weiger P. Erne Longterm Toxicology |
| Responsible for neurology: | Dr. sc. nat. W. Classen Neurotoxicology |
| Responsible for laboratory investigations: | Dr. med. vet. A. Waller, Dr. med. vet. P. Gretener FVH Clinical Chemistry Clinical Laboratory |
| Assistant laboratory investigations: | P. Letze Clinical Laboratory |
| Responsible for necropsy: | Dr. med. vet. M. Schoch, D.A.B.T. Macropathology |
| Responsible for pathology services: | PD Dr. med. vet. G. Winkler Pathology Services |
| Responsible for pathology: | Dr. med. vet. K. Heider FVH Pathology Head of Toxicologic Pathology |
| Responsible for neuropathology | G. J. Krinke, MVDr, C.Sc. FVH Pathology Experimental Pathology |
| Reviewing pathologist: | Dr. med. vet. Ch. Landes, FTA Pathology Toxicologic Pathology |
| Study pathologist: | Dr. med. vet. V. Pace, FVH Pathology Toxicologic Pathology |
| Responsible for statistics: | P. Christen, dipl.stat. Mathematical Applications |
| Responsible for analytics: | Dr. chem. H.P. Hornisch Analytical Development AD |

The job descriptions and the summaries of training and professional experience of personnel participating in this study are available at:

| | |
|---|---|
| CIBA-GEIGY Limited, 4332 Stein / Switzerland | for Short/Long-term Toxicology Sisseln Facility |
| CIBA-GEIGY Limited, 4002 Basle / Switzerland | for Short/Long-term Toxicology (Pathology) and Analytical Development AD and Mathematical Applications |

Archivation and distribution

Archives are located at CIBA-GEIGY Limited, Werk Stein WST 460, 4332 Stein / Switzerland. Raw data, protocol and report, specimens and raw data of laboratory investigations are stored at this location.

Raw data of the analytical determinations are stored in the archives of Analytical Development AD, CIBA-GEIGY Limited, 4002 Basle / Switzerland.

Raw data of the histopathological examination and specimens (wet tissues, tissue blocks or histological slides) are stored in the archives of Short/Long-term Toxicology (Pathology), CIBA-GEIGY Limited, 4002 Basle / Switzerland.

This report was distributed to:

Dr. H.J. Weideli (for the sponsor)

Archive

2. SUMMARY AND CONCLUSION

The test article TKA 40049 was administered by gavage for 4 weeks at daily doses of 0, 5, 25, 100 and 500 mg/kg bodyweight to a total of 140 albino rats. In each dose group 10 animals per sex and group (experimental group I) were sacrificed at the end of the treatment period. In the control group and in the highest dose group 10 animals per sex and group (experimental group II) were kept for a 4-week recovery period before sacrifice.

Administered quantities of the test article suspension were adjusted daily to individual bodyweight.

The results of this study are summarized as follows:

Mortality

No deaths occurred in this study.

In-life observations and neurological examinations

Clinical signs:

Shedding of the skin on the legs was observed in all high-dose animals and in females of group 4 and may be due to vasodilation of skin vessels.

Neurological examinations:

No changes of toxicological significance were observed in any of the parameters assessed.

Bodyweight

In both sexes, development of bodyweight was undisturbed by treatment.

Food consumption

The mean food consumption of all treated groups was comparable to that of the control group.

Food consumption ratios

The food consumption ratios calculated for treated groups were considered essentially comparable to those of the control group.

Hematology

The treatment at a high dose level of 500 mg/kg resulted in a slight and reversible increase of platelet counts. However, this finding was not considered to represent an adverse effect.

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Test Article: TKA 40049

Blood chemistry

At treatment end a dose-related inhibition of plasma cholinesterase was observed in males and females of groups 3, 4 and 5 (25, 100 and 500 mg/kg). Erythrocyte cholinesterase was inhibited in both sexes of group 5 (500 mg/kg) and in females of group 4 (100 mg/kg). Furthermore, brain cholinesterase was inhibited in female groups 4 and 5 (100 and 500 mg/kg). Effects on cholinesterase in plasma, erythrocytes and brain were reversible within the recovery period.

Higher gamma-glutamyl transpeptidase activities and minimally higher plasma cholesterol levels were recorded among high dose animals (500 mg/kg) at treatment end. Effects on plasma cholesterol were reversible.

Organ weights

Mean liver weights and mean liver to bodyweight ratios were increased in both sexes of group 5 (500 mg/kg) and in females of group 4 (100 mg/kg). At the end of recovery period full reversibility and partial reversibility were seen in group 5 males and females, respectively (500 mg/kg).

In females of group 5, a marked, statistically significant increase of mean absolute and relative adrenal weight was noted at treatment end. This effect was reversible within the recovery period.

Macroscopical findings

Macroscopically, enlarged livers were seen in 2/10 males and enlarged adrenal glands in 2/10 female rats of group 5 (500 mg/kg) at the end of the treatment period.

Microscopical findings

Microscopical examination showed the following treatment-related changes:

Minimal to moderate hypertrophy of the liver cells was observed in males and females of group 5.

Additionally, fatty change in males and cellular hypertrophy in females were seen in the adrenal cortex of animals of groups 4 and 5 (100 and 500 mg/kg). Within 4 weeks of recovery, both the liver and the adrenal gland changes were fully reversible.

Neuropathological examination provided no evidence of toxic neuropathy.

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Conclusion

Treatment with TKA 40049 resulted in dose-dependent, reversible inhibition of cholinesterases in brain, erythrocytes and plasma. Nevertheless, in-life observations, neurological examination and neuropathological examination did not reveal any indication of a potential neurotoxic effect related to the treatment. In addition, slight, but reversible adrenotropic and hepatotropic effects were found.

It can be inferred from the observations made during the above study, that a "no observable effect level" (NOEL) for TKA 40049 when offered to rats by daily gavage over a period of 4 weeks is 5 mg/kg. Based on the reversibility of findings and considering the absence of adverse consequences due to cholinesterase inhibition, the "no observable adverse effect level" (NOAEL) is regarded to be 500 mg/kg.

3. MATERIALS AND METHODS

3.1. Test article

| | |
|---------------------|---------------------|
| Company code No.: | TKA 40049 |
| Trade name: | CGI 403 |
| Batch No.: | FZ Marly-WSH, dried |
| Description: | solid, light yellow |
| Purity: | 93 % |
| Date of receipt: | August 14, 1992 |
| Stability: | June 1995 |
| Storage conditions: | room temperature |

Because of photosensitivity of TKA 40049, preparation and handling of suspensions were carried out under protection from light.

Pretest analytics

Prior to the start of the study, samples of the vehicle containing the test article at concentrations of 0.1, 1, 10 and 100 mg/ml were dispatched to the analytical laboratories of Analytical Development AD, CIBA-GEIGY Limited, 4002 Basle / Switzerland, for analysis of content, homogeneity and stability.

The results of the analyses (Analytical Report S-5/92) are given in the results and appendix sections of this report.

3.2. Test system

3.2.1. Experimental animals

Species: albino rats

Stock: Tif: RAIf (SPF),
hybrids of RII/1 x RII/2
(Sprague-Dawley derived)

Source: Animal Production
CIBA-GEIGY Limited
4332 Stein / Switzerland

Initial bodyweight:
(at week -1) 156.7 - 185.4 g in males
123.5 - 154.7 g in females

Initial age: approximately 5 weeks at delivery

3.2.2. Husbandry

The study was carried out under specified pathogen free (SPF) standard laboratory conditions. The animals were housed in groups of 5 in macrolon cages type 4 with wire mesh tops and standardized granulated soft wood bedding (Societe Parisienne des Sciures Pantin).

The animal room was air conditioned:

Temperature: $22 \pm 2^{\circ}\text{C}$

Relative humidity (%): 55 ± 10

Ventilation: 16-20 air changes/hour

Light cycle: 12 hours light per day

Neither insecticides nor chemicals were applied in the animal room with the exception of disinfectant: BRADOPHENTM.

3.2.3. Identification

By tattoo of tail for cage number and by tattoo of right ear auricle with numbers 1 to 5 for individual identification of the animals in the cages.

3.3. Procedures

A written protocol was prepared prior to the initiation of this study.

3.3.1. Study schedule

| | |
|---|-----------------------------------|
| Study initiation: | February 19, 1993 (protocol date) |
| Delivery of animals: | March 9, 1993 |
| Start of acclimatation: | March 10, 1993 |
| Treatment start: | March 17, 1993 |
| Neurological investigation: | April 13, 1993 |
| Laboratory investigations: | April 14-15, 1993 |
| Date of sacrifice 1: | April 15-16, 1993 |
| Recovery start: | April 14, 1993 |
| Neurological investigation: | May 11, 1993 |
| Laboratory investigations: | May 12, 1993 (recovery group) |
| Date of sacrifice 2 (experimental end date): | May 13, 1993 (recovery group) |

3.3.2. Animal number and distribution

Number of animals: 140 (total)
10 males, 10 females per dose group

plus 10 males and 10 females in the control and high dose group for recovery

The general outline of the experiment is presented in the following animal distribution table:

| Animal No. (cage no.) | Group 1 Control | Group 2 5 mg/kg | Group 3 25 mg/kg | Group 4 100 mg/kg | Group 5 500 mg/kg |
|--------------------------|--------------------|--------------------|---------------------|----------------------|----------------------|
| MALES I | 1-10 (1-2) | 21-30 (5-6) | 31-40 (7-8) | 41-50 (9-10) | 51-60 (11-12) |
| MALES II | 11-20 (3-4) | | | | 61-70 (13-14) |
| FEMALES I | 71-80 (15-16) | 91-100 (19-20) | 101-110 (21-22) | 111-120 (23-24) | 121-130 (25-26) |
| FEMALES II | 81-90 (17-18) | | | | 131-140 (27-28) |

I EXPERIMENTAL GROUP I

10 animals per sex and group for evaluation of toxicity, including neurology and laboratory investigations

II EXPERIMENTAL GROUP II

10 animals per sex and group (control and high dose group) for reversibility evaluation after 4 weeks of recovery, including neurology and laboratory investigations

3.3.3. Acclimatation

An acclimatation period of 7 days was allowed between delivery and start of the treatment. Immediately after delivery, the animals were distributed into groups. In order to set up a fully randomized experiment, they were assigned to these groups by means of computer-generated random numbers. Furthermore, they were weighed during this period.

From the same batch of animals a small number was retained for possible replacement during the acclimatation period. These animals were subjected to identical conditions during this period, and those not used were removed at the start of the experiment.

3.3.4. Treatment

The treatment was performed over a period of 4 weeks on a main group (experimental group I) and a recovery group (experimental group II) of animals. The animals of experimental group I were sacrificed at the end of the treatment period.

3.3.5. Recovery

After the treatment, animals of experimental group II were kept for a consecutive recovery phase of 4 weeks before sacrifice.

3.3.6. Rationale for dose selection

Dose levels were fixed based on the results of the following previously conducted study:

Project no. 924013
Short/Long-term Toxicology, CIBA-GEIGY Limited, Stein
Acute oral toxicity in the rat:

TKA 40049 was administered to 5 rats of either sex at dose levels of 2000, 1000, and 500 mg/kg bodyweight. All animals recovered within 3 days.

LD50 in rats of both sexes: greater than 2000 mg/kg bodyweight

and

Project no. 924165
Short/Long-term Toxicology, CIBA-GEIGY Limited, Stein
14-days range finding study in rats (gavage):

TKA 40049 was administered to 5 rats of either sex at dose levels of 10, 100, and 1000 mg/kg bodyweight per day.

Clinical signs observed at the high dose level included vasodilation (extremities and ears), hypoactivity, hunched posture, hypotonia, ataxia, chromorhinorrhea, and squamous skin on feet, scrotum and tail root, but all animals survived the treatment period. The final mean bodyweights in high dose males and females were depressed by 9 and 6%, respectively, and the overall mean food intake was reduced by 8 and 12%, respectively.

Hematological findings included increased platelet counts in high dose males and in high and intermediate dose females. A minimally increased neutrophils count was associated with a relative decrease in lymphocytes in high dose animals.

Inhibition of plasma cholinesterase was recorded in both sexes of the high and intermediate groups. Plasma protein and cholesterol concentration were increased in animals of the high dose group (1000 mg/kg), cholesterol additionally in males of group 3 (100 mg/kg). A minimally increased sodium concentration was noted in males of group 4 (1000 mg/kg).

Compared to control values the following organ weights showed changes: absolute and relative mean liver weights in group 3 and 4 males and in group 4 females were slightly to markedly increased in a dose-related manner; absolute and relative mean adrenal weights were slightly to markedly increased in group 4; absolute mean thymus weights in both sexes of groups 3 and 4 and thymus to bodyweight ratios in group 3 and 4 females were considered slightly reduced.

3.4. Test article administration and diet

Route of administration

The test article was administered orally by gavage.

Frequency of administration

1 dose per day, 7 times per week.

Preparation of suspension

Suspensions of the test article in the selected vehicle at the appropriate concentrations were freshly prepared every day immediately prior to the dosing of the animals and administered within 2 hours.

Vehicle

As a standard procedure, distilled water containing 0.5% carboxymethylcellulose and 0.1% Tween 80 was used as a vehicle.

Volume of suspension applied

10 ml/kg bodyweight

Control analyses

Control analyses of the test article concentration in the vehicle were carried out at all dose levels on samples collected once per experimental week. The samples were collected on completion of dosing, immediately deep-frozen and sent to Analytical Development AD, CIBA-GEIGY Limited, 4002 Basle / Switzerland. The results thereof (Analytical Report No. F-4/93) are given in the results and appendix sections of this report.

Control animals

The control animals were dosed in the same way as the treated rats with vehicle, without the test article.

3.4.1. Diet

Pelleted, certified standard diet (Nafag No. 890 Tox) was provided ad libitum (except as noted under Laboratory Investigations). All batches of diet were assayed for composition and contaminant levels by the manufacturer. Analytical results are available at the animal supply office (CIBA-GEIGY Limited, Pharmaceuticals Division).

3.4.2. Water

Tap water was given ad libitum. The drinking water quality fulfilled the critical parameters in the specifications of the "Schweizerisches Lebensmittelbuch" (Ed. 1972). The results of the routine chemical examination of water at source (Grundwasserfassung Stein) as conducted periodically by the water authority (Baudepartement des Kantons Aargau, Abteilung Gewaesserschutz) are available to CIBA-GEIGY Limited, as well as the results of inhouse chemical analysis by the analytical laboratories of the Pharmaceuticals Division, CIBA-GEIGY Limited.

3.5. Observations and records

Mortality

All animals were checked daily (a.m. and p.m. on working days, a.m. on weekends and holidays), in order to record mortalities, and to allow dead or moribund animals to be submitted to necropsy as soon as possible.

In-life observations

Examinations were carried out daily and observations were recorded at least weekly.

Assessment of clinical signs included observation of undisturbed animals in the homecage, during handling, and, if clinical signs have been observed, in a standard arena. Observations included, but were not limited to, signs of general appearance, alertness when undisturbed, reactivity to handling, autonomic signs, postural and gait abnormalities, and abnormal behavior.

Only positive findings irrespective of their toxicological significance are reported. Group means of clinical signs are presented as incidence rates. For assessment of a potential neurotoxic effect relevant clinical signs were sorted according to their physiological significance into observational groups as given in the table below. According to the following formula mean scores for each of the observational groups were calculated for each time period and normalized to a maximum score of 100:

$$\frac{\text{sum of scores} \times 100}{\text{maximal possible scores}}$$

| Observational groups | Clinical sign |
|-----------------------------|---|
| Sensorimotor | ataxia paresis |
| CNS activity | locomotor activity recumbency palpebral closure stereotypies |
| CNS excitability | convulsions cramps tremor fasciculations muscular tone posture/gait ease of removal ease of handling |

interdigital pads of the hindfeet². Individual data for grip strength and landing foot splay are means of two readings. In cases of insufficient collaboration by the animal or incorrect trials, readings were discarded and the measurement repeated.

Bodyweight

The weight of all animals was recorded individually at weekly (midweek) weighing sessions. The first weights were recorded during the acclimatation period. Daily bodyweights for accurate dosing were taken but not recorded.

Food consumption

The food consumption was recorded weekly (cagewise) and was calculated for periods of one week. The calculation was based on the weight of the offered diet at the beginning of a weighing period and its difference to the re-weighed amount after several days.

The individual food consumption values were calculated from the food consumption per cage and the number of animals present.

Food consumption ratios

The food consumption ratios were calculated as mean of individual ratios according to the following formula:

$$\frac{\text{weekly food consumption (g)}}{\text{midweek bodyweight (g)}} \times \frac{1000}{7}$$

Unit: g food/kg bodyweight per day

<2> EDWARD PM and PARKER VH. A simple, sensitive, and objective method for early assessment of acrylamid neuropathy in rats. Toxicol. Appl. Pharmacol. 40: 589-591, 1977

3.6. Laboratory investigations

Laboratory investigations (hematology, blood chemistry) were carried out on all surviving animals of each dose group at the end of the treatment period (April 14/15, 1993), and additionally at the end of the recovery period (May 12, 1993) on animals of the control and high dose group kept for reversibility evaluation. Determination of cholinesterase in brain and red blood cells was performed on 5 animals per sex and group at treatment end and at the end of the recovery period.

To reduce the biological variability due to circadian rhythms, blood sampling was performed in the morning. Food was withheld overnight prior to blood removal. Ether anesthesia was used to restrain the animals. Blood was withdrawn from the orbital sinus using glass capillary tubes.

Blood samples from each animal with the respective anticoagulant (EDTA for performing the complete blood count, 3.8% Sodium citrate for coagulation testing, Heparin for blood chemistry and methemoglobin measurements) were collected into individual vials. Samples of brain were collected at necropsy, frozen immediately and maintained for cholinesterase determination.

The parameters and methods used are listed in the following tables.

3.6.1. Parameters and methods used in hematology

Parameters determined by the Technicon H*1 <1>, <2>
(Method code: M0002)

| Red blood cell parameters | Abbreviation | Unit |
|--|--------------|-----------|
| Erythrocyte count | RBC | T/l |
| Hemoglobin | Hb | mmol/l |
| Hematocrit | Hct | l |
| Mean corpuscular volume | MCV | fl |
| Red cell volume distribution width<3> | RDW | l |
| Mean corpuscular hemoglobin | MCH | fmol |
| Mean corpuscular hemoglobin concentration | MCHC | mmol/l |
| Hemoglobin concentration distribution width<3> | HDW | mmol/l |
| White blood cell parameters | | |
| Leukocyte count | WBC | G/l |
| Differential leukocyte count | | rel. abs. |
| Neutrophils | Neut | l G/l |
| Eosinophils | Eos | l G/l |
| Basophils | Baso | l G/l |
| Lymphocytes | Lympho | l G/l |
| Monocytes | Mono | l G/l |
| Large unstained cells | Luc | l G/l |
| Blood platelets | | |
| Thrombocyte Count | Plt | G/l |
| <u>Prothrombin time</u> | | |
| Photometric assay using chromogenic substrate on a Cobas Bio centrifugal analyser (Method code: M0001) | PT (CS) | sec |
| <u>Mathemoglobin</u> | | |
| Determined spectrophotometrically using a Hemoximeter OSM 3 (Method code: M0001) | MethHb | l |

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References

- <1> D.T. Davies, G.V. Fisher (1991): The Validation and Application of the Technicon H*1 for the Complete Automated Evaluation of Laboratory Animal Haematology
Comp Haematol Int 1, 91-105
- <2> W. Groner, J. Boyett, A. Johnson, M. Scantlebury (1986): Variability of Erythrocyte Size and Hemoglobin Content Observed in Man and Four Selected Mammals
Blood Cells 12, 65-80
- <3> C. Fossat et al. (1987): New Parameters in Erythrocyte Counting
Arch Pathol Lab Med 111, 1150-1154

3.6.2. Parameters and methods used in blood chemistry

| Parameter | Method of analysis (Method code) Instrument | Abbreviation | Unit |
|-----------------|---|--------------|--------|
| Glucose | Hexokinase/G6P-DH (M0001) HITACHI 737 | Gluc | mmol/l |
| Urea | Urease/GLDH (M0001) HITACHI 737 | Urea | mmol/l |
| Creatinine | Enzymatic colorimetric test (M0001) HITACHI 737 | Creat-e | umol/l |
| Total bilirubin | Reaction with 2,5-Di- chlorophenyldiazonium salt (M0001) HITACHI 737 | Bili-tot | umol/l |
| Total protein | Biuret reaction (M0001) HITACHI 737 | Prot | g/l |
| Albumin | Bromcresol green method (M0001) HITACHI 737 | Alb | g/l |
| Globulins | Calculated value (M0001) (Total Protein minus Albumin) | Glob | g/l |
| A/G Ratio | Calculated value (M0001) (Albumin/Globulins) | A/G | 1 |
| Cholesterol | Enzymatic, CHOD/PAP (M0001) HITACHI 737 | Chol | mmol/l |
| Triglycerides | Glycerol-Kinase GPO/PAP method (M0001) HITACHI 737 | Trigly | mmol/l |
| Sodium | Ion selective electrode (M0001) HITACHI 737 | Na+ | mmol/l |
| Potassium | Ion selective electrode (M0001) HITACHI 737 | K+ | mmol/l |
| Calcium | o-Cresolphthalein complexone method (M0001) HITACHI 737 | Ca++ | mmol/l |

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| Parameter | Method of analysis (Method code) Instrument | Abbreviation | Unit |
|--|---|--------------|--------|
| Chloride | Ion selective electrode (M0001) HITACHI 737 | Cl- | mmol/l |
| Phosphorus inorganic | Phosphomolybdate reaction (M0001) HITACHI 737 | PO4-in | mmol/l |
| Aspartate amino- transferase EC 2.6.1.1 | MDH/NADH coupled reaction method (M0001) HITACHI 737 | ASAT (GOT) | U/l |
| Alanine amino- transferase EC 2.6.1.2 | LDH/NADH coupled reaction method (M0001) HITACHI 737 | ALAT (GPT) | U/l |
| Alkaline phosphatase EC 3.1.3.1 | p-Nitrophenyl-phosphate as substrate (M0001) HITACHI 737 | AlP | U/l |
| Gamma-glutamyl transpeptidase EC 2.3.2.2 | Substrate: L-gamma- glutamyl-3-carboxy- 4-nitroanilide (M0001) HITACHI 737 | GGT | U/l |
| Cholinesterase (Plasma) EC 3.1.1.8 | Substrate: Butyryl- thiocholine (M0001) HITACHI 737 | ChE-P1 | U/l |
| Cholinesterase (RBC) EC 3.1.1.7 | Substrate: Acetyl- thiocholine (M0002) COBAS BIO | ChE-RBC | U/l |
| Cholinesterase (Brain) EC 3.1.1.7 | Substrate: Acetyl- thiocholine (M0002) UVIKON 930 | ChE-Br | U/g |

3.7. Pathology

3.7.1. Macroscopical examination

At the end of the treatment period all controls and treated animals of experimental group I, and at the end of the recovery period, all animals of experimental group II, were bled under ether anesthesia and subjected to detailed necropsy.

At necropsy the following weights were recorded from all animals:

- body (exsanguinated)
- brain
- liver
- kidneys
- adrenals
- ovaries/testes

The following organs and tissues were preserved in neutral buffered 4% formalin:

- skin
- mammary area
- spleen
- mesenteric lymph node
- axillary lymph node
- sternum with bone marrow
- femur with joint
- skeletal muscle
- trachea
- lung
- heart
- aorta
- submandibular salivary gland, both
- liver
- pancreas
- esophagus
- stomach
- small intestine
- large intestine
- kidney, both
- urinary bladder
- prostate
- seminal vesicle
- testis, both
- epididymis, both
- uterus
- vagina
- ovary, both
- pituitary gland
- adrenal gland, both
- thyroid with parathyroid gland
- thymus

peripheral nerve
brain
spinal cord
eye with optic nerve, both
orbital gland, both
extraorbital lacrimal gland, both
Zymbal gland, both
muzzle
tongue
any tissue with gross lesions

3.7.2. Microscopical examination

After the fixation, organ samples listed below were taken from all animals of the control and all treated groups (experimental group I) embedded in paraplast, sectioned at 3-5 microns, stained with hematoxylin and eosin, and subjected to a microscopical examination:

spleen
heart
liver
kidney, both
adrenal gland, both
any organ with gross lesions

In addition, since the examination of the experimental group I revealed treatment-related changes in the liver and the adrenal gland, these organs were processed and examined also in experimental group II.

For neuropathological examination, the samples listed below were taken from all animals of the control and high-dose groups (experimental groups I and II) and processed to hematoxylin-eosin stained paraffin sections as described above:

brain (the available half of forebrain, center of cerebrum, midbrain, cerebellum, and pons)
spinal cord (cervical and lumbar level including lumbar dorsal and ventral spinal roots)
peripheral nerve (sciatic)
eye with optic nerve, both

3.7.3. Presentation of pathology data

Where practicable, gross lesions were identified by a capital letter, e.g. A, B, C, etc. at necropsy.

At the subsequent histopathological evaluation the diagnosis or diagnoses corresponding to the macroscopically identified lesions were given the same alphabetical label in order to correlate the microscopical findings with the changes seen at necropsy.

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The relationship between primary and secondary diagnosis was indicated by an arrow, e.g. B -> A, specifying that the diagnosis "B" was secondary to the diagnosis recognized as "A".

The microscopical findings were assessed with respect to their severity as well as their incidence (number of affected individuals per group). The summary tables presented in this report show the incidence of microscopical lesions, while the severity of each particular lesion (with exceptions specified by the valid standard operating procedures) is described with the individual findings. The degree of severity was assessed according to the following criteria:

Grade "+" : Minimal. Includes histopathological change that is a noticeable but not prominent feature of the tissue.

Grade "++" : Moderate. Includes histopathological change that is a prominent but not dominant feature of the tissue.

Grade "+++" : Marked. Includes histopathological change that is a dominant feature of the tissue.

3.8. Statistical analysis

For each time point and parameter an univariate statistical analysis was performed. Nonparametric methods <1> were applied, to allow for non normal as well as normal data distribution.

Each treated group was compared to the control group by Lepage's <2> two-sample test and tested for increasing or decreasing trends from control up to the respective dose group by Jonckheere's test for ordered alternatives <3>. The Lepage test is a combination of Wilcoxon and Ansari-Bradley statistics, i.e. a combined test for location and dispersion. The Lepage test has a good power against the more general alternative that the distributions differ not only in location but also in dispersion. The Jonckheere test is sensitive to monotone dose-related effects.

Two-sided asymptotic p-values are reported in the "statistics" tables. Flags for significant differences between groups (*) or trends over groups (+ or -) are given in the "means" tables according to the specified significance level. Statistical tests and flags used are indicated in the header of each table.

Measurements from neurological investigations from each treated group were compared to the control group using the Wilcoxon Rank Sum test <4>; exact p-values are given in the statistics table. Increasing or decreasing trends in location from control to the highest dose group were tested by Jonckheere's test using the Monte-Carlo estimate of p-values based on 2000 samples.

Statistical significance does not necessarily imply biological relevance. Hence, the responsible scientist may not comment on statistically significant values lying within the physiological range and on the other hand may comment on values, which differ substantially from the expected normal values although this difference was not statistically significant.

References

- <1> E.L. Lehmann, Nonparametrics: Statistical Methods Based on Ranks. Holden-Day (1975): pp. 5-31, 95, 232-238
- <2> Y. Lepage, Biometrika (1971) 58: pp. 213-217
- <3> A.R. Jonckheere, Biometrika (1954) 41: pp. 133-145
- <4> StatXacttm (V 1.0), Cytel Software Corp. Cambridge, Ma, USA

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Explanation of statistics and flags

N the number of observations on which the calculations are based

Mean the sum of the observed values divided by N

Median the 50th percentile

IQ-Range the interquartile range, the difference between the 75th and the 25th percentile

Min, Max the smallest value, the largest value

p_L p-value, the probability of an outcome being greater than or equal to Lepage's test statistic, if the null hypothesis is true. Not given, if sample sizes too small

*****, significant difference in location and/or dispersion between treated group and control at the level specified in the header of the table

a, indicative of a difference in location

b, indicative of a difference in dispersion

p_J p-value, the probability of an outcome being greater than or equal to the absolute value of Jonckheere's standardized test statistic, if the null hypothesis is true (two-sided, no correction for ties). Not given, if sample sizes too small

+ or -, significant positive or negative trend from control up to the respective dose group at the level specified in the header of the table

3.9. Deviations

3.9.1. Amended

Amendment 1 (date of issue: March 29, 1993)

Deviating from the protocol, the determination of erythrocyte cholinesterase and brain cholinesterase activities was performed on a limited number of animals, due to technical reasons.

Determination of erythrocyte cholinesterase

The activity of erythrocyte cholinesterase was determined in the animals specified in the table below.

| Animal no. | Group 1 control | Group 2 5 mg/kg | Group 3 25 mg/kg | Group 4 100 mg/kg | Group 5 500 mg/kg |
|------------|--------------------|--------------------|---------------------|----------------------|----------------------|
| Males | 16-20 | 26-30 | 36-40 | 46-50 | 66-70 |
| Females | 86-90 | 96-100 | 106-110 | 116-120 | 136-140 |

Determination of brain cholinesterase

Determination of brain cholinesterase activity was performed in the animals specified in the following table.

| Animal no. | Group 1 control | Group 2 5 mg/kg | Group 3 25 mg/kg | Group 4 100 mg/kg | Group 5 500 mg/kg |
|-------------------------|--------------------|--------------------|---------------------|----------------------|----------------------|
| Males, Exp. grp. I | 6-10 | 26-30 | 36-40 | 46-50 | 56-60 |
| Exp. grp. II | 16-20 | | | | 66-70 |
| Females, Exp. grp. I | 76-80 | 96-100 | 106-110 | 116-120 | 126-130 |
| Exp. grp. II | 86-90 | | | | 136-140 |

3.9.2. Not amended

In addition to the date proposed in the protocol, the neurological investigations were also performed towards the end of recovery period (May 11, 1993).

During the study, Dr. A. Waller (responsible for laboratory investigations) was replaced by Dr. P. Gretener.

The above mentioned deviation is considered to have no impact on the validity of the study.

There were no deviations and no known circumstances that could have affected the quality and/or integrity of the data.

4. RESULTS

4.1. Analytical results

Prior to the beginning of the study, suspensions containing the test article at concentrations of 0.1, 1.0, 10 and 100 mg/ml were analyzed for determination of content, homogeneity and stability.

The results of these analyses showed that the contents of TKA 40049 in the vehicle were in agreement with the nominal concentrations and that the samples were homogeneous and stable for 2 hours at room temperature (Analytical Report S-5/92, see Appendix B of this report).

In this study, as shown in the table below, the calculated mean contents of TKA 40049 in the vehicle were 86, 98, 107 and 103% of the nominal concentrations in dose groups 2, 3, 4 and 5, respectively (Analytical Report F-4/93, see Appendix B of this report).

TEST MATERIAL CONTENT

| CONTENT | GROUP 2 | GROUP 3 | GROUP 4 | GROUP 5 |
|--------------------|-------------|---------|-----------|---------|
| NOMINAL (mg/ml) | 0.5 | 2.5 | 10 | 50 |
| ANALYTICAL (mg/ml) | | | | |
| study week: 1 | 0.368/0.165 | 2.49 | 19.4/5.05 | 50.2 |
| 2 | 0.495 | 2.46 | 10.1 | 51.7 |
| 3 | 0.481 | 2.49 | 10.4 | 52.0 |
| 4 | 0.471 | 2.39 | 10.1 | 51.3 |
| ----- | ----- | ----- | ----- | ----- |
| MEAN, WEEK 1-4 (%) | 85.7 | 98.3 | 107 | 103 |

4.2. In-life observations

The clinical signs observed in the course of the study are presented in the appendix section of this report and in the following summary table. Identical observations occurring repeatedly in the same animal are indicated only once in the summary table.

Shedding of skin on hindlegs and forelegs was observed in all high-dose animals and in 8 of 10 females of group 4. In high-dose animals this sign appeared on day 6 and was observed for about 3 to 9 days. In group 4 females the onset was slightly later with comparable duration. Skin shedding may be secondary to vasodilation of skin vessels and thus may indicate autonomic stimulation.

Other findings were not considered to be related to treatment with the test article.

INCIDENCES OF IN-LIFE OBSERVATIONS

| OBSERVATIONS | males | | | | | females | | | | | |
|-------------------|--------|----|---|---|---|---------|----|----|---|---|----|
| | Group: | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| eye, exudate | | 1 | - | 1 | - | - | - | - | - | - | - |
| eye, injured | | - | - | - | - | - | - | - | 1 | - | - |
| hair loss | | 1 | - | - | - | - | - | - | - | - | 1 |
| mass | | - | - | - | - | - | - | - | - | - | 1 |
| skin lesion | | 4 | 1 | 2 | 1 | 1 | - | - | - | - | - |
| skin, squamous | | - | - | - | - | 20 | - | - | - | 8 | 20 |
| no findings noted | | 14 | 9 | 7 | 9 | 0 | 20 | 10 | 9 | 2 | 0 |

No clinical signs relevant for the assessment of a potential neurotoxic effect were seen throughout the study. Therefore evaluation by functional domains as described in the methods section was not performed.

4.3. Neurological examinations

Mean values from neurological examinations are presented in the following tables and plots. The individual values collected during the study and the results of the statistical analysis of these data are filed in the appendix sections of this report.

No changes of toxicological significance were observed in any of the parameters assessed.

Neurology (mean scores):

males

| | group 1 0 mg/kg | group 2 5 mg/kg | group 3 25 mg/kg | group 4 100 mg/kg | group 5 500 mg/kg |
|--|--------------------|--------------------|---------------------|----------------------|----------------------|
| | N | N | N | N | N |
| Hearing response (-1)^a | | | | | |
| week 4 | 20 | - ^b 10 | 10 | 10 | 20 |
| week 8 | 10 | - | 10 | 10 | 10 |
| Pain reflex (±2) | | | | | |
| week 4 | 20 | - | 10 | 10 | 20 |
| week 8 | 10 | - | 10 | 10 | 10 |
| Visual placing (-1) | | | | | |
| week 4 | 20 | - | 10 | 10 | 20 |
| week 8 | 10 | - | 10 | 10 | 10 |
| Righting responses (-1) | | | | | |
| week 4 | 20 | - | 10 | 10 | 20 |
| week 8 | 10 | - | 10 | 10 | 10 |
| Pupillary reflexes (-1) | | | | | |
| week 4 | 20 | - | 10 | 10 | 20 |
| week 8 | 10 | - | 10 | 10 | 10 |

^a maximal score
^b - = normal

Neurology (means):

males

| | group 1 0 mg/kg | group 2 5 mg/kg | group 3 25 mg/kg | group 4 100 mg/kg | group 5 500 mg/kg |
|-----------------------------------|--------------------|--------------------|---------------------|----------------------|----------------------|
| | N | N | N | N | N |
| body temperature (°C) | | | | | |
| week 4 | 20 39.1 | 10 38.6 | 10 38.7 | 10 38.7 | 20 38.6 |
| week 8 | 10 39.1 | | | | 10 39.1 |
| grip strength forepaws (g) | | | | | |
| week 4 | 20 1101 | 10 1081 | 10 1099 | 10 1055 | 20 1045 |
| week 8 | 10 975 | | | | 10 1079 |
| grip strength hindpaws (g) | | | | | |
| week 4 | 20 1148 | 10 1158 | 10 1162 | 10 1173 | 20 1159 |
| week 8 | 10 1045 | | | | 10 1112 |
| Landing foot splay (cm) | | | | | |
| week 4 | 20 10.4 | 10 10.5 | 10 9.3 | 10 8.9 | 20 9.8 |
| week 8 | 10 11.8 | | | | 10 12.2 |

+/- p < .01 Jonckheere Trend Test, two-sided (group 1 to 5)
 * p < .01 Wilcoxon Rank Sum Test, exact, two-sided

Neurology (mean scores):

females

| | group 1 0 mg/kg | group 2 5 mg/kg | group 3 25 mg/kg | group 4 100 mg/kg | group 5 500 mg/kg |
|--|--------------------|--------------------|---------------------|----------------------|----------------------|
| | N | N | N | N | N |
| Hearing response (-1)^a | | | | | |
| week 4 | 20 | - ^b 10 | 10 | 10 | 20 |
| week 8 | 10 | - | | | 10 |
| Pain reflex (± 2) | | | | | |
| week 4 | 20 | - 10 | 10 | 10 | 20 |
| week 8 | 10 | - | | | 10 |
| Visual placing (-1) | | | | | |
| week 4 | 20 | - 10 | 10 | 10 | 20 |
| week 8 | 10 | - | | | 10 |
| Fighting responses (-1) | | | | | |
| week 4 | 20 | - 10 | 10 | 10 | 20 |
| week 8 | 10 | - | | | 10 |
| Pupillary reflexes (-1) | | | | | |
| week 4 | 20 | - 10 | 10 | 10 | 20 |
| week 8 | 10 | - | | | 10 |

^a maximal score
^b - = normal

Neurology (means):

females

| | group 1 0 mg/kg | group 2 5 mg/kg | group 3 25 mg/kg | group 4 100 mg/kg | group 5 500 mg/kg |
|-----------------------------------|--------------------|--------------------|---------------------|----------------------|----------------------|
| | N | N | N | N | N |
| body temperature (°C) | | | | | |
| week 4 | 20 38.4 | 10 38.2 | 10 38.6 | 10 38.8 | 20 38.4 |
| week 8 | 10 39.1 | | | | 10 39.2 |
| grip strength forepaws (g) | | | | | |
| week 4 | 20 991 | 10 1044 | 10 1133 * | 10 1088 | 20 1004 |
| week 8 | 10 1162 | | | | 10 1026 |
| grip strength hindpaws (g) | | | | | |
| week 4 | 20 921 | 10 1043 | 10 1072 * | 10 1088 * | 20 1029 * |
| week 8 | 10 1020 | | | | 10 927 |
| Landing foot splay (cm) | | | | | |
| week 4 | 20 9.1 | 10 8.7 | 10 8.9 | 10 8.8 | 20 8.5 |
| week 8 | 10 10.4 | | | | 10 8.6 |

+/- p < .01 Jonckheere Trend Test, two-sided (group 1 to 5)
 * p < .01 Wilcoxon Rank Sum Test, exact, two-sided

4.4. Mortality

No deaths occurred in this study.

4.5. Bodyweight

Mean bodyweight values are presented in the following tables and plots. The individual bodyweight values collected during the study and the results of the statistical analysis of these data are filed in the appendix sections of this report.

In both sexes, development of bodyweight was undisturbed by treatment.

Triage of 8(e) Submissions

Date sent to triage: 11-22-96

NON-CAP

CAP

Submission number: 12752 A

TSCA Inventory:

Y

N

D

Study type (circle appropriate):

Group 1 - Gordon Cash (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN

w/NEUR

Group 3 -HERD (1 copy each)

STOX CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

- This is the original 8(e) submission; refile after triage evaluation.
- This original submission has been split; rejoin after triage evaluation.
- Other:

| Photocopies Needed for Triage Evaluation | | | | |
|--|-------------|---|---|---|
| entire document: | 0 | 1 | 2 | 3 |
| front section and CECATS: | 0 | 1 | 2 | 3 |
| Initials: _____ | Date: _____ | | | |

CECATS DATA: Submission # BEHQ-1193-12752 SEQ. A

CECATS/TRIAGE TRACKING DBASE ENTRY FORM

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: Ciba-Geigy Corporation

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)
DISPOSITION:
0639 REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED/IN PROGRESS
0403 NOTIFICATION OF WORKING METHODS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 11/15/93 OTS DATE: 11/17/93

CSRAD DATE: 06/28/96

CHEMICAL NAME: Phosphine Oxide, Bis(2,6-Dimethoxybenzoyl) Case
2,4,4-Trimethylpentyl-
CGI 403

145052-34-2
" "

INFORMATION TYPE:

| | | P F C |
|-------------|--------------------------|----------------|
| 0201 | ONCO (HUMAN) | 01 02 04 |
| 0202 | ONCO (ANIMAL) | 01 02 04 |
| 0203 | CELL TRANS (IN VITRO) | 01 02 04 |
| 0204 | MUTA (IN VITRO) | 01 02 04 |
| 0205 | MUTA (IN VIVO) | 01 02 04 |
| 0206 | REPRO/TERATO (HUMAN) | 01 02 04 |
| 0207 | REPRO/TERATO (ANIMAL) | 01 02 04 |
| 0208 | NEURO (HUMAN) | 01 02 04 |
| <u>0209</u> | NEURO (ANIMAL) | 01 <u>0</u> 04 |
| 0210 | ACUTE TOX. (HUMAN) | 01 02 04 |
| 0211 | CHR. TOX. (HUMAN) | 01 02 04 |
| 0212 | ACUTE TOX. (ANIMAL) | 01 02 04 |
| <u>0213</u> | SUB ACUTE TOX (ANIMAL) | 01 <u>0</u> 04 |
| 0214 | SUB CHRONIC TOX (ANIMAL) | 01 02 04 |
| 0215 | CHRONIC TOX (ANIMAL) | 01 02 04 |

INFORMATION TYPE:

| | | P F C |
|-------------|---------------------------|----------------|
| 0216 | EPI/CLIN | 01 02 04 |
| 0217 | HUMAN EXPOS (PROD CONTAM) | 01 02 04 |
| 0218 | HUMAN EXPOS (ACCIDENTAL) | 01 02 04 |
| 0219 | HUMAN EXPOS (MONITORING) | 01 02 04 |
| 0220 | ECO/AQUA TOX | 01 02 04 |
| 0221 | ENV. OCCUREL/FATE | 01 02 04 |
| 0222 | EMER INCI OF ENV CONTAM | 01 02 04 |
| 0223 | RESPONSE REQEST DELAY | 01 02 04 |
| <u>0224</u> | PROD/COMP/CHEM ID | 01 <u>0</u> 04 |
| 0225 | REPORTING RATIONALE | 01 02 04 |
| 0226 | CONFIDENTIAL | 01 02 04 |
| 0227 | ALLERG (HUMAN) | 01 02 04 |
| 0228 | ALLERG (ANIMAL) | 01 02 04 |
| 0239 | METAB/PHARMACO (ANIMAL) | 01 02 04 |
| 0240 | METAB/PHARMACO (HUMAN) | 01 02 04 |

INFORMATION TYPE:

| | | P F C |
|-------------|-------------------|----------|
| 0241 | IMMUNO (ANIMAL) | 01 02 04 |
| 0242 | IMMUNO (HUMAN) | 01 02 04 |
| <u>0243</u> | CHEM/PHYS PROP | 01 02 04 |
| 0244 | CLASTO (IN VITRO) | 01 02 04 |
| 0245 | CLASTO (ANIMAL) | 01 02 04 |
| 0246 | CLASTO (HUMAN) | 01 02 04 |
| 0247 | DNA DAM/REPAIR | 01 02 04 |
| <u>0248</u> | PROD/USE/PROC | 01 02 04 |
| 0251 | MSDS | 01 02 04 |
| 0299 | OTHER | 01 02 04 |

IRIAGE DATA: NON-CBI INVENTORY

ONGOING REVIEW

SPECIES

TOXICOLOGICAL CONCERN:

CAS SR

NO

YES (DROP/REFER)

RAT

LOW

USE:

PRODUCTION:

NO

NO (CONTINUE)

MED

photoinitiator
for coatings

IN TRAINING

REFER

HIGH

UNCLASSIFIED

PMN P93-0495

Reviewed
(M)

✓
"12752A"="M"="SUBACUTE ORAL TOXICITY IN THE RAT IS OF MEDIUM CONCERN. ALBINO RATS (10/SEX/DOSE) RECEIVED GAVAGE DOSES OF 0, 5, 25, 100, OR 500 MG/KG DAILY FOR 28 DAYS. AN ADDITIONAL 10 ANIMALS/SEX RECEIVED 0 OR 500 MG/KG FOR 28 DAYS FOLLOWED BY A 4 WEEK RECOVERY PERIOD. NO DEATHS OCCURRED. SHEDDING OF THE SKIN ON HINDLEGS AND FORELEGS WAS OBSERVED IN ALL HIGH-DOSE ANIMALS AND IN 8 OF 10 FEMALES AT 100 MG/KG. SKIN SHEDDING MAY BE SECONDARY TO VASODILATION OF SKIN VESSELS AND THUS MAY INDICATE AUTONOMIC STIMULATION. INHIBITION OF PLASMA CHOLINESTERASE WAS OBSERVED IN MALES AND FEMALES AT 25, 100, AND 500 MG/KG. ERYTHROCYTE CHOLINESTERASE WAS INHIBITED IN BOTH SEXES AT 500 MG/KG AND IN FEMALES AT 100 MG/KG. BRAIN CHOLINESTERASE WAS INHIBITED IN FEMALES AT 100 AND 500 MG/KG. EFFECTS ON CHOLINESTERASE IN PLASMA, ERYTHROCYTES AND BRAIN WERE REVERSIBLE WITHIN THE RECOVERY PERIOD. DATA ON PERCENT INHIBITION OF CHOLINESTERASE ACTIVITY WERE NOT PROVIDED. MEAN LIVER WEIGHTS AND MEAN LIVER TO BODY WEIGHT RATIOS WERE INCREASED IN BOTH SEXES AT 500 MG/KG AND IN FEMALES AT 100 MG/KG. AT THE END OF THE RECOVERY PERIOD FULL REVERSIBILITY AND PARTIAL REVERSIBILITY WERE SEEN AT 500 MG/KG IN MALES AND FEMALES, RESPECTIVELY. IN FEMALES AT 500 MG/KG, AN INCREASE OF MEAN ABSOLUTE AND RELATIVE ADRENAL WEIGHT WAS NOTED AT TREATMENT END. THIS EFFECT WAS REVERSIBLE WITHIN THE RECOVERY PERIOD. MACROSCOPICALLY, ENLARGED LIVERS WERE SEEN IN 2/10 MALES AND ENLARGED ADRENAL GLANDS IN 2/10 FEMALE RATS AT 500 MG/KG. MICROSCOPIC EXAMINATION REVEALED MINIMAL TO MODERATE HYPERTROPHY OF THE LIVER CELLS IN MALES AND FEMALES AT 500 MG/KG. FATTY CHANGES IN MALES AND CELLULAR HYPERTROPHY IN FEMALES WERE SEEN IN THE ADRENAL CORTEX OF ANIMALS AT 100 AND 500 MG/KG. BOTH THE LIVER AND THE ADRENAL GLAND CHANGES WERE FULLY REVERSIBLE AT THE END OF THE RECOVERY PERIOD. THE NOEL AND NOAEL WERE CONSIDERED TO BY 5 MG/KG AND 500 MG/KG, RESPECTIVELY."