UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

005692

12/29/86

MEMORANDUM

SUBJECT: Baygon (Propoxur) Toxicity Studies

TO: Mr. Dennis Edwards, PM 12
Registration Division (TS-767C)

FROM: Byron T. Backus
Toxicologist
Toxicology Branch (TS-769C)

THROUGH: Marcia van Gemert, Ph.D.
Section Head, Section III
Toxicology Branch (TS-769C)

and
Theodore Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Chemical no. 508

Project No. 1260 Record No. 165337

Action Requested:

In a memorandum dated December 23, 1985 R. Zendzian stated that the Registration Division should formally submit to TB for review the data package filed under accession no. 256151. This material was submitted to the TB on January 15, 1986.

Comments and Conclusions:

1. Some of the studies in this package had been previously reviewed by the Toxicology Branch (see the review of October 17, 1979 by W. Dykstra, Coberly file no. 003690). Of these studies three (an acute oral LD_{50} study, #75-144, dated August 26, 1976, on the use dilution of a 70% WP formulation; 1976; an acute oral LD_{50} study, #77-252, dated March 10, 1978, on a 70% WP formulation; and an acute dermal LD_{50} study, #77-252, dated March 21, 1978, on the 70% WP formulation) were previously classified as minimum, and there is no reason to change any of these classifications.

2. Two mutagenicity studies (a Rec assay and an Ames assay, both conducted at the Nitokung Agricultural Chemicals Institute in Japan, dated February 24, 1978) in this package had also pre-

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viously been reviewed by W. Dykstra (October 17, 1979), and had been classified as acceptable. Reexamination of these studies using current criteria for evaluation has, however, resulted in reclassifications of both to "not acceptable." Refer to DER XXI for further information.

3. The major report in this package was a chronic (12-month) dog feeding (dietary) study. This study has been classified as supplementary for the following two reasons:

   i) A NOEL was not observed as the lowest-dose (200 ppm) dogs showed significantly elevated mean plasma cholesterol levels at 13, 26 and 52 weeks relative to controls. Further, at these times the elevations were part of dose-related trends. It is disquieting that while the mean cholesterol levels in median-dose (600 ppm) and high-dose dogs were reported as being statistically significantly different from those of controls on these dates, those of the 200 ppm dogs were not.

   ii) There was a 100% incidence of atrophy of the thymus in high-dose dogs, along with a reduced mean weight of this organ in this group. 2/6 of the males in the median-dose group showed somewhat reduced mean thymus weights. Histopathology was only reported on dogs from the control and high-dose groups. There should have been histopathology reports on the thymus from median dose dogs, and if any possible effect had been noted from that group, from low-dose dogs as well.

   The findings from this 12-month study are considered valid, despite the current supplementary classification.

Data Evaluation Reports (attached):

The following is a listing of the individual data evaluation reports, along with the study classification. Copies should be supplied to the registrant.

I. Acute oral LD_{50} (propoxur 98.6%) - rat. Bayer AG Institute of Toxicology, report #11329, dated 12/15/82. Core supplementary data.

II. Acute intraperitoneal LD_{50} (propoxur 98.6%) - rat. Bayer AG Institute of Toxicology, report #11329, dated 12/15/82. Core supplementary data.

III. Cholinesterase (technical and recrystallized propoxur, 98.6 and 99.2% active respectively) - rat. Bayer AG Institute of Toxicology, report #11330, dated 12/15/82. Core supplementary data.

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IV. Cholinesterase & excretion of metabolite (propoxur 2%) human inhalation exposure. Bayer AG Institute of Toxicology, report #7554, dated 05/78. Core supplementary data.

V. Cholinesterase & excretion of metabolite ("chemically pure" propoxur) rat inhalation exposure. Bayer AG Institute of Toxicology, report #7555, dated 05/78. Core supplementary data.

VI. Primary dermal irritation (propoxur 99.2%) - rabbit. Bayer AG Institute of Toxicology, report #82229, dated 09/20/78. Core minimum data.

VII. Primary eye irritation (propoxur 99.2%) - rabbit. Bayer AG Institute of Toxicology, report #82229, dated 09/20/78. Core minimum data.

VIII. Acute oral LD_{50} (Baygon 0.5% aqueous) - rat. Stanley Research Center, report 81-011-05, dated 07/31/81. Core minimum data.

IX. Acute oral LD_{50} (Baygon 2% bait) - rat. Stanley Research Center, #79 AOR 10, dated 09/03/80. Core supplementary data.

X. Acute dermal LD_{50} (Baygon 0.5% aqueous) - rabbit. Stanley Research Center, report #81-023-05, dated 06/22/81. Core minimum data.

XI. Acute dermal LD_{50} (Baygon 2% bait) - rabbit. Stanley Research Center, report #81-023-01, dated 04/13/81. Core minimum data.

XII. Acute inhalation LC_{50} (Baygon 0.5% aqueous) - rat. Stanley Research Center, report #81-041-12, dated 10/11/82. Core minimum data.

XIII. Acute inhalation LC_{50} (Baygon 2% bait) - rat. Stanley Research Center, report #81-041-01, dated 09/25/81. Core supplementary data.

XIV. Primary eye irritation (Baygon 0.5% aqueous) - rabbit. Stanley Research Center, report #81-333-15, dated 10/06/81. Core minimum data.

XV. Primary dermal irritation (Baygon 0.5% aqueous) - rabbit. Stanley Research Center, report #81-323-16, dated 10/06/81. Core minimum data.

XVI. Primary eye irritation (Baygon 2% bait) - rabbit. Stanley Research Center, report #81-333-04, dated 04/13/81. Core minimum data.

XVII. Primary dermal irritation (Baygon 2% bait) - rabbit. Stanley Research Center, report #81-323-04, dated 04/13/81. Core minimum data.

XVIII. Use exposure (BAYTEX 93% LC) - human. Mobay Chemical Corporation, #53115, dated 03/76. Core supplementary data.

XIX. 5-day oral dosage & enzyme induction (technical grade and recrystallized propoxur, 98.6 & 99.2% active respectively) - rat. Bayer AG Institute of Toxicology, #11621, dated 03/08/83. Core supplementary data.

XX. Chronic (12-month) feeding (propoxur 99.4%) - dog. Bayer AG Institute of Toxicology, #12605, dated 04/11/84. Core supplementary data.

XXI. Mutagenicity, rec assay (propoxur 98%) - B. subtilis. Nitokung Agricultural Chemicals Institute (Japan), report #103, dated 02/24/78. Not acceptable.

Mutagenicity, Ames assay (propoxur 98%) - S. typhimurium. Nitokung Agricultural Chemicals Institute (Japan), report #103, dated 02/24/78. Not acceptable. mentary data.

XXII. Mutagenicity, in vivo micronucleus (Baygon, 99.2%) - mouse. Bayer AG Institute of Toxicology, EHR file #2347, dated 06/27/80. Acceptable.

XXIII. Mutagenicity, Ames assay (technical 98.6%) - S. typhimurium. Bayer AG Institute of Toxicology, report # 11301, dated 12/06/82. Acceptable.

XXIV. Mutagenicity, POL (DNA repair) assay (technical 98.5-98.6%) - E. coli. Bayer AG Institute of Toxicology, report #11403, dated 01/06/83. Not acceptable.

XXV. Mutagenicity, Ames assay (propoxur 98%) - S. typhimurium and WP2 hcr E. coli. Institute of Toxicology (Japan), report #84124, dated 02/28/83. Acceptable.

Mutagenicity, Rec assay (propoxur 98%) - B. subtilis. Institute of Toxicology (Japan), report #84124, dated 02/28/83. Not acceptable.

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XXVI. 5-day oral dosage & enzyme induction (propoxur 99.4%) - rat. Bayer AG Institute of Toxicology, #10976, dated 06/29/82. Core supplementary data.

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Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D. 12.17.86
Section 3, Tox. Branch (TS-769C)

DATA EVALUATION REPORT I

STUDY TYPE: Acute oral LD_{50} - Rat TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: Carbamate UN

SYNONYMS: 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): Report no. 11329

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Carbamate UN, Technical - Study for Acute Toxicity on Rats.

AUTHOR(S): Heimann, K.-G.

REPORT ISSUED: 12/15/82

CLASSIFICATION: Core supplementary data

CONCLUSIONS:

1. The rat oral LD_{50}'s reported in this study (fasted males, 69 mg/kg; fasted females, 47 mg/kg; unfasted males, 167 mg/kg, and unfasted females, 96 mg/kg) can be accepted.

2. The study is, however, classified as supplementary data because of a lack of reporting of a considerable amount of substantive data (including - but not limited to - body weights, when individual rats died, individual necropsy results).

A. MATERIALS:

1. Test compound: Carbamate UN technical, 98.6% active ingredient, no physical description, identified as a mixture of 5 batches (100201, 100216, 100222, 100226, 100234).

2. Test animals: Wistar albino rats, approx. 160-200 g, from Winkelmann in Borchen.

B. STUDY DESIGN:

1. Animal assignment: not stated. Groups of 10 fasted ("unfed") males were dosed at 1, 5, 25, 50, 63, 71, 80, 90, 100 and 160 mg/kg. Groups of 10 fasted females were dosed

at 1, 5, 10, 40, 50, 63 and 80 mg/kg. Groups of 10 unfasted males were dosed at 10, 25, 100, 125, 160, 180, 200, 250 and 400 mg/kg; and groups of 10 unfasted females at 10, 25, 50, 80 (there were 20 females at this level), 90, 100, 125 and 200 mg/kg.

2. Test material preparation and administration: the test material was mixed with polyethylene glycol 400, and this mixture was administered via stomach tube in a volume of 0.5 ml/100 g of body weight.

3. Statistics: the mean lethal dose (LD_{50}) was calculated by the method of Litchfield and Wilcoxon.

4. Quality assurance: no quality assurance statement is provided.

C. METHODS AND RESULTS:

1. Observations:

Rats were observed for 14 days after dosing. From reporting of when mortalities first occurred it appears that rats were inspected for death at 1 and 2 hours after dosage.

Toxicity

Symptoms included convulsions, spastic gait, dacryohaemorrhea, bristling coat and apathy. Tremors were apparently observed only in fasted rats, and at doses above 5 mg/kg. No symptoms were observed in fasted rats which received 1 mg/kg of the test material, or in unfasted rats which had been dosed at 10 mg/kg. All the other rats showed some sort of symptoms. "Surviving animals" were apathetic for up to 8 days.

Cholinergic symptoms (convulsions, tremors, dacryohaemorrhea) were observed for several hours after dosage; spastic gait and bristling coat were observed for up to 6 days after dosing.

Mortality

The lowest dosage levels at which deaths occurred in fasted rats were 50 mg/kg for males (2/10 dying) and 40 mg/kg for females (2/10 dying). For unfasted rats the lowest dose levels were at which mortality occurred were 125 mg/kg for males (2/10 dead) and 80 mg/kg for females (4/20 dead). "Onset" of death was, even for many of the lower dose groups at which mortality occurred, 1 or 2 hrs after dosage. However, it is reported (probably erroneously) in table 2 that onset of death was 6 days in females at the highest dose level (200 mg/kg).

The oral LD_{50}'s are reported as the following:

males, fasted	=	69 (60-79) mg/kg
females, fasted	=	47 (42-53) mg/kg
males, unfasted	=	167 (146-192) mg/kg
females, unfasted	=	96 (87-106) mg/kg

It is not reported anywhere what the values in parenthesis represent. However, since higher values are slightly farther from the reported LD_{50} than are lower values, they probably represent the 95% confidence limits

2. Body weight

No body weight data (either on a group mean or individual basis) are reported.

3. Necropsies

Rats dying during the study are reported as having a patchy (and/or?) distended lung and dark liver. No individual results are given.

Animals sacrificed at the end of the observation period had internal organs showing "no macroscopic damage attributable to the test sample."

D. DISCUSSION:

The lack of a considerable amount of substantive data (including - but not limited to - body weights, when rats died, individual necropsy results) is a disappointment, particularly considering the number of rats used in this study.

Because these data were not reported the report has to be classified as supplementary.

Reviewed by: Byron T. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) M. van Gemert 12.12.86

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DATA EVALUATION REPORT II

STUDY TYPE: Acute Intraperitoneal LD_{50} - Rat TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: Carbamate UN

SYNONYMS: 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): Report no. 11329

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Carbamate UN, Technical - Study for Acute Toxicity on Rats.

AUTHOR(S): Heimann, K.-G.

REPORT ISSUED: 12/15/82

CLASSIFICATION: Core supplementary data

CONCLUSIONS:

1. The rat intraperitoneal LD_{50}'s reported in this study (males, 16 mg/kg; females, 13 mg/kg) can be accepted.

2. While the report provides some relevant information regarding the toxicity of Propoxur when administered by the intraperitoneal route, this type of study is not normally specified as a data requirement. It is also noted that there is some lack of substantive data (including individual body weight data, ages of test animals, individual necropsy results). Overall then the study is classified as core supplementary.

3. If the rats receiving Propoxur in PEG 400 suspension weighed 160-200 grams, then they were injected with 0.8 to 1.0 mls ("animals received 0.5 ml solution per 100 g body weight"), while controls were dosed with 5 mls PEG 400. It is noteworthy that no information is given regarding the severity (or incidences) of the swollen livers and adhesions of liver lobes which are attributed to the PEG 400. Of course, the question could also be asked as to why a vehicle which could elicit a toxic effect by itself was used.

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A. MATERIALS:

1. Test compound: Carbamate UN technical, 98.6% active ingredient, no physical description, identified as a mixture of 5 batches (100201, 100216, 100222, 100226, 100234).

2. Test animals: Wistar albino rats, approx. 160-200 g, from Winkelmann in Borchen.

B. STUDY DESIGN:

1. Animal assignment: not stated. The material was injected into the abdominal cavities. Groups of 10 males received 1, 8, 10, 12.5, 14, 20, 25 (20 males), 31.5 or 35.5 mg/kg of the test material; groups of 10 females received 1, 5, 10, 12.5, 16 or 100(!) mg/kg. There were control rats (5 males, 5 females) which each received an IP injection of 5 ml PEG 400.

2. Test material preparation and administration: the test material was mixed with polyethylene glycol 400, and the concentrations were such that rats received 0.5 ml of the suspension per 100 g of body weight.

3. Statistics: the mean lethal dose (LD_{50}) was calculated by the method of Litchfield and Wilcoxon.

4. Quality assurance: no quality assurance statement is provided.

C. METHODS AND RESULTS:

1. Observations:

From reporting of when mortalities first occurred it appears that rats were inspected for death at 30 minutes and 1 hr after dosage. Rats were observed for 14 days.

Toxicity

Cholinergic symptoms ("the same as those after oral administration," which would presumably then include convulsions and tremors) were observed. There is no indication as to when these symptoms began or when they subsided.

Mortality

Some mortalities occurred in all groups receiving more than 10 mg/kg. The intraperitoneal LD_{50} is reported as 16 (14-20) mg/kg in males, and as 13 (11-15 mg/kg) in females. It is not reported what the values in parenthesis stand for, but this reviewer considers it probable that they represent the 95% confidence limits.

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2. Body weights

No body weight data (either on a group mean or individual basis) are reported.

3. Necropsies

"Dissection of the animals dying during the study and those sacrificed at end . . . revealed swollen livers and some adhesions of the liver lobes. The animals administered only polyethylene glycol 400 intraperitoneally produced the same findings on dissection..."

D. DISCUSSION:

The values given for the intraperitoneal LD_{50}'s are valid. This study is not normally required by the Agency, as it is difficult to envisage a situation where human exposure could occur by this route.

If the rats receiving Propoxur in PEG 400 suspension weighed 160-200 grams, then they were injected with 0.8 to 1.0 mls ("animals received 0.5 ml solution per 100 g body weight"), while controls were dosed with 5 mls PEG 400. It is noteworthy that no information is given regarding the severity (or incidences) of the swollen livers and adhesions of liver lobes which are attributed to the PEG 400. Of course, the question could also be asked as to why a vehicle which could elicit a toxic effect by itself was used.

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DATA EVALUATION REPORT III

STUDY TYPE: Cholinesterase - Rat

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: Carbamate UN

SYNONYMS: 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): Report no. 11330

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Carbamate UN, Technical Product: Acute Study of the Effect on the Activity of the Cholinesterases in Blood Plasma, Erythrocytes and Brains of Rats Compared with Carbamate UN Recrystallised Product.

AUTHOR(S): Heimann, K.-G.

REPORT ISSUED: 12/15/82

CLASSIFICATION: Core supplementary data

CONCLUSIONS:

1. The study demonstrates considerable, but temporary, inhibition of plasma and brain ChE (about 50% in each case) in rats orally dosed at 25 mg/kg, with no unequivocal effects on RBC ChE (a drop of 10-15% could have been masked by normal fluctuations in this parameter). Recovery of plasma ChE to preexposure levels occurred by 3 hours after dosage, and of brain ChE by day 3. No ChE effects were observed at 1 and 5 mg/kg.

2. It is not stated whether ChE values for a given time and dose represent measurements obtained from a pooled sample or a mean of 5 individual determinations. No information is given as to ages of rats or whether they were fasted before dosing. The study is therefore classified as supplementary.

A. MATERIALS:

1. Test compound: Carbamate UN technical, 98.6% active ingredient, no physical description, identified as a mixture of 5 batches (100201, 100216, 100222, 100226, 100234). Carbamate UN, recrystallised product, mixture of 5 batches (001222-001226), 99.2% "content."

2. Test animals: Wistar albino rats WISW (SPF-CPB), approx. 160-200 g, from Winkelmann in Borchen.

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B. STUDY DESIGN:

1. Animal assignment: not stated. In the first test series, groups of males orally received 1, 5 or 25 mg/kg of either the 98.6% active material or the recrystallised product with 99.2%. In two subsequent tests (one with the 98.6% active material, the other with 99.2% recrystallised product) groups of males and females orally received dosages of 1, 5 or 25 mg/kg test material. No indication is given as to whether or not rats were fasted before being dosed.

2. Test material preparation and administration: the test material was mixed with polyethylene glycol 400, and this mixture was administered via stomach tube. Concentrations were adjusted so that the volume given was kept at 0.5 ml per 100 g of body weight.

3. Statistics: there is no indication that any statistical methods were used.

4. Quality assurance: no quality assurance statement is provided.

C. METHODS AND RESULTS:

1. ChE activities:

Blood was taken from the plexus retroorbitalis and plasma and RBC ChE activities were determined. Some rats were sacrificed (exsanguination by heart puncture under diethyl ether narcosis) and brain ChE (one page of the report states "cholinesterase," another page states "acetylcholinesterase") was measured. Activities were determined by a modified Ellmann method. In the first test series plasma and RBC ChE activities were determined at 0, 3, 5 and 24 hours, and at 3, 7 and 14 days. Brain "ChE" activity was determined at 5 hours and at 14 days. In subsequent tests blood plasma and RBC ChE activities were determined for 0, 30 and 60 minutes, 3, 5 and 24 hours and at 3 days. Brain "ChE" was determined at 1 and 3 hours and at 3 days.

"Cholinesterase activities were determined for five animals per point in time and dose."

Results

No symptoms were observed in rats receiving 1 or 5 mg/kg of the test material. Those dosed at 25 mg/kg had convulsions, reduced motility, apathy and "bristling coat," with recovery taking up to 2 days.

For cholinesterase activities, no data from individual rats are presented, only group values. It is uncertain whether these values are means calculated from individual measurements, or whether the blood and/or brain samples were pooled

before ChE activities were measured.

In the first series of ChE measurements (first post-dosage ChE values at 3 hours) there were no indications of plasma and/or RBC activity inhibition. At 5 hours the brain AChE activity in the 25 mg/kg group was 13.3% below the 0 hr value for controls (a 5 hr value was not done for controls), but a similar simultaneous "depression" occurred in rats of the 1 mg/kg group (but not 5 mg/kg).

In subsequent testing, dosage with 25 mg/kg of either 98.6% material or the 99.2% recrystallised product resulted in pronounced temporary plasma and brain ChE inhibitions (approximately 50% in each case); with recovery of plasma ChE activity at 3 hours after dosage, and recovery of brain "ChE" at 3 days. This reviewer's interpretation of the RBC ChE data is that, given the normal fluctuations in this parameter, there was no conclusive evidence of inhibition; although it could have been present at perhaps 10-15%.

PLASMA ChE

Substance tested	Sex	Activities in terms of Pre-exposure value: 30 minutes	60 minutes	3 hours
98.6% technical	M	0.50	0.54	1.00
99.2% recrystallised	M	0.48	0.48	1.02
98.6% technical	F	0.81	0.74	1.04
99.2% recrystallised	F	0.58	0.51	1.03

RBC ChE

Substance tested	Sex	Activities in terms of Pre-exposure value: 30 minutes	60 minutes	3 hours
98.6% technical	M	0.72	0.73	0.80
99.2% recrystallised	M	0.74	0.69	0.71
98.6% technical	F	0.98	0.92	1.07
99.2% recrystallised	F	0.88	0.88	1.06

Brain ChE

Substance tested	Sex	Activities in terms of Pre-exposure value: 60 minutes	3 hours	3 days
98.6% technical	M	0.53	0.85	1.12
99.2% recrystallised	M	0.65	0.73	1.29
98.6% technical	F	0.45	0.77	1.06
99.2% recrystallised	F	0.40	0.96	1.15

There was no evidence for plasma, RBC or brain ChE inhibition at the lower dose levels (1 and 5 mg/kg).

D. DISCUSSION:

The study has some value in demonstrating a considerable - and temporary - inhibition (of about 50%) for plasma and brain ChE activities in rats following oral dosage at 25 mg/kg. No unequivocal effect was observed on RBC ChE, although it is possible that this parameter may have fallen by 10 or 15%, which would have been easily masked by normal fluctuations in this parameter. No effects could be seen at lower dose levels (1 and 5 mg/kg).

However there are some uncertainties because of gaps in the data reporting. As indicated earlier in this review it is not specified whether ChE values for a given time and dose level represent a mean of 5 individual determinations, or results obtained by measuring ChE activities on a pooled sample. No information is presented as to the approximate ages of these rats, or whether they were even fasted before dosing. The study is therefore classified as supplementary.

Reviewed by: Byron Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D. M van Gemert 12.17.86
Section 3, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT IV

STUDY TYPE: Cholinesterase & Excretion of a metabolite - human

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: Propoxur

SYNONYMS: 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): Report no. 7554

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Propoxur - Single Exposure of Persons to Propoxur with Determination of Acetylcholinesterase Activity in Plasma and Erythrocytes, Propoxur Concentration in Blood and Elimination of 2-Isopropoxyphenol in Urine.

AUTHOR(S): Kimmerle, G. and Eben, A.

REPORT ISSUED: May 1978

CLASSIFICATION: Core supplementary data

CONCLUSIONS:

1. Following 4-hr human exposure to air containing 3 $\pm$ 1.8 mg/m^3 propoxur, there were no indications of any RBC or plasma AChE inhibition. No propoxur was detected in blood samples.

2. 2-Isopropoxyphenol (a metabolite of propoxur) was detected in urine collections, with a cumulative total of from 1.6 to 3.7 mg/person. A mean of 65.7% of the total measured amount was excreted in the period from 0-8 hrs, and 34.3% in 8-24 hrs. 3/4 of the subjects had "traces" of 2-isopropoxyphenol in their 24-48 collections.

A. MATERIALS:

1. Test compound: 2% Propoxur [redacted] Packaged in aerosol cans.

2. Subjects: Three men and one woman, aged 25-50 years.

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B. STUDY DESIGN:

1. Four human subjects were exposed for 4 hrs in a 15 m^3 room to an average propoxur concentration of 3.0 ± 1.8 mg/m^3.

2. Test material administration: the concentration was produced and maintained by spraying the aerosol cans for periods of 2 seconds each at commencement of exposure and thereafter at 20 minute intervals.

3. Statistics: the only parameter to which statistics was apparemtly applied was the mean concentration of propoxur in the room (reported as 3 ± 1.8 mg/m^3). However, individual analyses ("performed at 10 minute intervals") are not reported.

4. Quality assurance: there is no quality assurance statement.

C. METHODS AND RESULTS:

1. AChE activities:

Blood samples (used for plasma and RBC AChE determinations) were taken prior to exposure, and at 0, 0.5, 1 and 2 hrs after exposure termination, and individual subject values for these parameters were measured and reported. An attempt was also made to measure the amount of propoxur in blood.

Results

There was no indication of any plasma or RBC AChE inhibition. No propoxur was detected in the blood.

2. 2-Isopropoxyphenol in the Urine:

Urine output from each individual was taken for the intervals of 0-8, 8-24, 24-48 and 48-72 hrs after start of exposure. Urine specimens were analyzed for 2-isopropoxyphenol (a metabolite of propoxur).

Results

Total amounts of 1.6 to 3.7 mg 2-isopropoxyphenol/person were detected in the urine collections. A mean of 65.7% of the total measured amount was excreted in the 0-8 hr samplings, and 34.3% in the 8-24 hr samplings. 3/4 individuals had "traces" in the 24-48 collections.

D. DISCUSSION:

The lack of any effects on plasma or RBC AChE activities is not surprising, as the total intake of propoxur for each individual was probably well below 1 mg/kg. However, as no data are reported regarding individual body weights, or how much total propoxur was sprayed in the room a more exact "guessti-

mate" cannot be made.

The study does demonstrate that, at least at these low levels and by this exposure route, some propoxur is metabolized and excreted as 2-isopropoxyphenol fairly rapidly.

It is not understood why blood samples were not analyzed for 2-isopropoxyphenol rather than (or in addition to) propoxur.

Overall, the study is classified as supplementary.

Reviewed by: Byron [redacted] Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) Marcia van Gemert 12.17.86

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DATA EVALUATION REPORT V

STUDY TYPE: Cholinesterase - Rat

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: Propoxur

SYNONYMS: 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): Report no. 7555

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Acute Inhalation Study on Rats with Determination of Acetylcholinesterase Activity in Blood and Elimination of 2-isopropoxyphenol in Urine.

AUTHOR(S): Kimmerle, G., and Eben, A.

REPORT ISSUED: May 1978

CLASSIFICATION: Core supplementary data

CONCLUSIONS:

1. The value of this study is very limited without the following information, which should be provided:

   i) individual values for plasma and erythrocyte AChE activities, as well as how the baseline was determined.

   ii) whether the values given for 2-isopropoxyphenol excre-excretion represent mean individual values, or whether they are group totals for the periods indicated. The limit of analytical detection for 2-isopropoxyphenol should also be reported.

   iii) urine analyses results for the individual rats should be reported if urine samples were not pooled by group.

A. MATERIALS:

1. Test compound: "Use was made of chemically pure propoxur."

2. Test animals: Wistar albino rats SPF, 160-180 g from Winkelmann in Borchen.

B. STUDY DESIGN:

1. Animal assignment: not stated. There were 10 males and 10 females per exposure group.

2. Test material preparation and exposure: the test material was dissolved in a mixture of polyethylene glycol 400 and absolute ethanol (1:1), and aerosolized in a dynamic flow inhalation apparatus. Propoxur concentrations were 0.4, 1.2, 9, 30, 78 and 172 mg/m^3 of air. Exposure was for 6 hours.

3. Statistics: there is no indication that any statistical methods were used.

4. Quality assurance: no quality assurance statement is provided.

C. METHODS AND RESULTS:

1. Acetylcholinesterase (AChE) activities:

Following exposure blood was taken from 5 rats/sex/dose and plasma and RBC AChE activities were determined using a modification of a colorimetric method of Pilz.

Results

For AChE activities, no data from individual rats are given, only group values. These are designated as "means from 5 rats per dose."

The following values for "depression" (there is no indication of how or whether a baseline was established) of AChE are reported in table 2:

Propoxur concentration in mg/m^3	Percent depression of AChE after termination of exposure	
	Plasma	Erythrocytes
	Male Rats	
0.4	-	-
1.2	-	-
9	-	-
30	19.3	12.8
78	29.2	39.0
172	44.0	31.7
	Female Rats	
0.4	-	-
1.2	-	-
9	-	-
30	14.9	7.3
78	17.5	24.1
172	31.2	35.1

The statement is made: "it is evident that depression of plasma and erythrocyte cholinesterase activities was clearly measurable only at concentrations of 172 and 78 mg propoxur/m^3.

2. 2-isopropoxyphenol concentrations in urine:

"On termination of exposure, all the rats were placed in metabolism cages for 3 days. The concentration of 2-isopropoxyphenol was determined in the 24-hour urine collected from each of 10 male rats and 10 female rats per group."

Results

The following is taken from table 1:

Propoxur concentration in mg/m^3	0.4	1.2	9	30	78	172
Days after termination of exposure	2-isopropoxyphenol, ug/24 hours					
		Male rats				
1	2.4	3.8	14.5	65	89	192
2	-	-	2.5	9	22	59
3	-	-	-	-	10	21
Total	2.4	3.8	17.0	74	121	272
		Female rats				
1	2.6	3.8	12.2	33	83	216
2	-	-	2.8	7	21	37
3	-	-	-		13	16
Total	2.6	3.8	15.0	40	117	269

There is no indication as to whether these are mean values or cumulative group totals. Also, no value is given for the limit of detection of isopropoxyphenol.

3. Symptoms:

Rats exposed to 172 mg/m^3 are reported as having had "general health impairment" and "cholinergic symptoms which occurred 30 minutes after commencement of inhalation," with rapid recovery after termination of exposure.

D. DISCUSSION:

The value of this study is very limited without the following information:

i) individual values for plasma and erythrocyte AChE activities, as well as how the baseline was determined.

ii) whether the values given for 2-isopropoxyphenol excre-excretion represent mean individual values, or whether they are group totals for the periods indicated. The limit of analytical detection for 2-isopropoxyphenol should also be reported.

iii) urine analyses for the individual rats should be reported, if group pooling of urine samples was not done

Overall, the study is classified as supplementary.

Reviewed by: Byron C. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) M van Gemert 12.11.86

005692

DATA EVALUATION REPORT VI

STUDY TYPE: Primary dermal irritation-rabbit TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: Propoxur technical (BOE 5812315)

SYNONYMS: 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): Report no. 82229

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Propoxur - Studies on the Irritant Effect on Skin and Mucous Membrane

AUTHOR(S): Thysser, J. and Lorke, D.

REPORT ISSUED: 09/20/78

CLASSIFICATION: Core minimum data

CONCLUSIONS:

1. The results (PDIS = 0.0 following 24-hr exposure) indicate the test material is in toxicity category IV in terms of its ability to cause dermal irritation.

A. MATERIALS:

1. Test compound: Propoxur technical, 99.2% "purity" Tot no. 2028.

2. Test animals: New Zealand white rabbits, 3-4 kg, from Hacking, Huntingdon, England.

B. STUDY DESIGN:

1. Animal assignment: not stated. Six animals were used.

2. Test material administration: "tests were conducted following the recommended guidelines of the U.S. Department of Agriculture (Federal Register, 38, 187:27019, 1973). Exposure time was 24 hours."

3. Quality assurance: no quality assurance statement is provided.

C. METHODS AND RESULTS:

1. Observations:

Individual scores for erythema and edema were read for intact and abraded sites at 24 and 72 hours.

Results

All sites scored zero at 24 and 72 hours. PDIS = 0.0.

D. DISCUSSION:

The results (PDIS = 0.0 following 24-hr exposure) indicate the test material has a low hazard potential (toxicity category IV) in terms of its ability to cause dermal irritation.

Reviewed by: Byron Backus
Section 3, Tox. Branch (TS-769C)

005692

Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) 12.17.86

DATA EVALUATION REPORT VII

STUDY TYPE: Primary eye irrication - rabbit TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: Propoxur technical (BOE 5812315)

SYNONYMS: 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): Report no. 82229

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Propoxur - Studies on the Irritant Effect on Skin and Mucous Membrane

AUTHOR(S): Thyssen, J. and Lorke, D.

REPORT ISSUED: 09/20/78

CLASSIFICATION: Core minimum data

CONCLUSIONS:

1. The results (only minimal conjunctival redness in the 2/3 unwashed eyes at 24 hrs, clearing by 48 hrs) indicate the test material is in toxicity category IV in terms of its eye irritation potential.

A. MATERIALS:

1. Test compound: Propoxur technical, 99.2% "purity" lot no. 2028.

2. Test animals: New Zealand white rabbits, 3-4 kg, from Hacking, Huntingdon, England.

B. STUDY DESIGN:

1. Animal assignment: not stated. Eight animals were used.

2. Test material administration: "tests were conducted using the recommended guidelines of the U.S. Department of Health, Education and Welfare (Fed. Reg., 37, 83:8535, 1972)." Exposure times were 5 minutes (for 5 eyes) and 24 hours (3 eyes).

3. Quality assurance: no quality assurance statement is provided.

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C. METHODS AND RESULTS:

1. Observations:

Eyes were scored at 1, 24, 48, 72 hrs and 7 days.

Results

4/5 of the eyes which were exposed for 5 minutes showed minimal conjunctival redness at 1 hr, but all were clear at subsequent readings. 2/3 of the eyes exposed for 24 hrs had minimal conjunctival redness at 24 hrs, but were clear at 48 hrs. There were no signs of corneal involvement.

D. DISCUSSION:

Most of the eyes scored "1" for conjunctival redness at 24 hrs (and this was the maximum degree of irritation observed). According to the November 1982 Subdivision F Hazard Evaluation Guidelines (p. 54) a score of 2 or more for conjunctival redness indicates a positive effect.

The results indicate then the test material has a low hazard potential (toxicity category IV) in terms of its ability to cause eye irritation.

Reviewed by: Byron [redacted]. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C)

005692

DATA EVALUATION REPORT VIII

STUDY TYPE: Acute oral LD_{50} - Rat

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: Baygon 0.5% Aqueous

SYNONYMS: 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): 81-011-05

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Stanley Research Center

TITLE OF REPORT: Acute Oral Toxicity of Baygon 0.5% Aqueous to Rats

AUTHOR(S): Hixson, E. J.

REPORT ISSUED: 07/31/81

CLASSIFICATION: Core minimum data

CONCLUSIONS:

1. The rat oral LD_{50} value for an 0.5% Baygon in water formulation was greater than 5000 mg/kg for both male and female rats. The NOEL was 1250 mg/kg for males and 625 mg/kg in females.

A. MATERIALS:

1. Test compound: Baygon 0.5% Aqueous, with actual A.I. reported as 0.5%. Batch no. 81-R-17-33.

2. Test animals: Sprague-Dawley derived rats, from Sasco Inc., Omaha, Nebraska. Males ranged from 311-482 g, and females from 218-281 g.

B. STUDY DESIGN:

1. Animal assignment: not stated. Groups of 5 males and 5 females (fasted for 19 hrs) received 1250, 2500 or 5000 mg/kg of the test material. An additional group of 5 females received 625 mg/kg.

2. Test material preparation and administration: "The excipient used for administering the test material was Carbowax."

3. Quality assurance: a statement is made (p. 6 of the report) that "This report has been reviewed by the department's Quality Assurance Unit."

C. METHODS AND RESULTS:

1. Observations:

Rats were observed at 0.5, 1 and 4 hrs posttreatment and twice daily for 14 days after dosing.

Toxicity:

Symptoms included tremors and decreased activity. For groups with symptoms at least some of the animals were affected at 0.5 hrs after dosage. Symptoms were no longer present in these groups on day 1. There were no symptoms in males at 1250 mg/kg, or in females at 625 mg/kg.

Mortality:

No mortality occurred at any dose level.

2. Body weight:

Animals were weighed on days 0, 7 and 14.

Results:

Average group body weights increased (no individual body weights are reported) over the 2-week observation period.

3. Necropsies:

Survivors were sacrificed on day 14 and were examined for gross lesions.

Results:

"No gross lesions that could be related to treatment were observed at day 14 sacrifice."

D. DISCUSSION:

The study indicates a low hazard potential (toxicity category IV) for this 0.5% Baygon formulation when received by the oral exposure route. This is not surprising, as even at the highest dose level rats were receiving only 25 mg/kg of the active ingredient.

The study is acceptable as core minimum data.

Reviewed by: Byron E. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) 12.17.86

005692

DATA EVALUATION REPORT IX

STUDY TYPE: Acute oral LD_{50} - Rat

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: Baygon 2% Bait

SYNONYMS: 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): 79 AOR 10

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Stanley Research Center

TITLE OF REPORT: Acute Oral Toxicity of Baygon 2% Bait to Rats

AUTHOR(S): Lamb, D. W., Hixson, E. J., Toll, P. A., Mallicoat, D. R., Schroeder, R. S.

REPORT ISSUED: 09/03/80

CLASSIFICATION: Core Supplementary Data

CONCLUSIONS:

1. The oral LD_{50} of this 2% Baygon formulation is greater than 500 mg/kg when given by gavage, and there were no symptoms or mortality in rats receiving more than 50,000 ppm (= 1,000 ppm Baygon) in their food for 24 hours.

A. MATERIALS:

1. Test compound: Baygon 2% Bait, with actual A.I. reported as 2.0%. Batch no. 9030074.

2. Test animals: Sprague-Dawley derived rats, from Sasco Inc., Omaha, Nebraska. Males ranged from 190-380 g, and females from 162-263 g.

B. STUDY DESIGN:

1. Animal assignment: not stated. In the attempts to administer the test material by gavage there were 5 males and 5 (or 4) females per dose level. The test material was given by gelatin capsule to 10 males. Subsequently, there were 10 males and 10 females per dose level when the test material was offered as part of the diet at 10,000 and 50,000 ppm. Rats were fasted for 19 hours before being given the test material.

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2. Test material preparation and administration: In the first attempt to orally administer the test material the "excipient" was Carbowax. A stainless steel feeding needle was used to give doses of 60 (females only), 105, 184, 322 and 563 mg/kg (males only), and a polyethylene catheter was used to give a dose of 500 mg/kg. Subsequently, an attempt was made to administer the test material by capsule to males at doses varying (according to individual rat weights) of from 284 to 404 mg/kg. Treated feed (Purina Lab Chowetts) containing 10,000 or 50,000 ppm of the test material (mixed with corn oil) was then offered for 24 hours to fasted rats.

3. Statistics: There is no indication of any use of statistical methods other than what appears to be a standard deviation for average consumption of formulation-treated feed.

4. Quality assurance: there is no quality assurance statement.

C. METHODS AND RESULTS:

1. Observations:

Rats were observed at 0.5, 1 and 4 hrs posttreatment and twice daily for 14 days after dosing.

Toxicity:

Unspecified symptoms were observed in 2/5 males receiving 563 mg/kg by feeding needle, and in 5/5 males receiving 500 mg/kg by catheter. No symptoms were observed in females receiving the test material by feeding needle (Highest dose = 322 mg/kg), but all 4 females receiving 500 mg/kg by polyethylene catheter are reported as having (unspecified) symptoms. No symptoms occurred in rats feeding on 10,000 or 50,000 ppm of the test material (50,000 ppm test material = 1,000 ppm Baygon); at 50,000 ppm average amounts of test material consumed were 2012 $\pm$ 673 mg/kg for males and 1795 $\pm$ 374 mg/kg for females.

Mortality:

Mortality occurred in 1/5 males receiving 563 mg/kg by feeding needle, and in 1/4 females receiving 500 mg/kg by catheter. All males dosed with gelatin capsules died; necropsies showed the capsules had stuck in or punctured the esophagus.

2. Body weight:

Animals were weighed on days 0, 7 and 14.

Results:

Average group body weights increased (no individual body weights are reported) over the 2-week observation period.

3. Necropsies:

Survivors were sacrificed on day 14 and were examined for gross lesions.

Results:

"No gross lesions that could be related to treatment were observed at day 14 sacrifice."

D. DISCUSSION:

It is noted (p. 7) that accuracy of the doses administered, particularly at the higher levels, were questionable because the suspension could hardly be forced through the feeding needle or catheter. The only information that could be obtained was that the oral LD_{50} was greater than 500 mg/kg. The feeding study simply indicated that that the LC_{50} for a 2% Baygon formulation was in excess of 50,000 ppm (= 1,000 ppm Baygon). As chronic feeding studies have been submitted to the Agency demonstrating that 5000 ppm Baygon can be fed to rats, the lack of any indication of mortality and/or toxicity in this short-term study is hardly surprising.

The study is classified as supplementary.

Reviewed by: Byron [redacted]. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) M van Gemert 12.17.86

005692

DATA EVALUATION REPORT X

STUDY TYPE: Acute dermal LD_{50} - Rabbit TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: Baygon 0.5% Aqueous

SYNONYMS: 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): 81-023-05

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Stanley Research Center

TITLE OF REPORT: Acute Dermal Toxicity of ®BAYGON 0.5% Aqueous

AUTHOR(S): Lamb, D. W., Hixson, E. J., English, T. D., Mallicoat, D. R., Schroeder, R. S.

REPORT ISSUED: 06/22/81

CLASSIFICATION: Core minimum data

CONCLUSIONS:

1. The study indicates a low hazard potential (toxicity category III) for this formulation in terms of its dermal toxicity (no mortality or signs of toxicity at 2000 mg/kg; dermal LD_{50} > 2000 mg/kg).

A. MATERIALS:

1. Test compound: Baygon 0.5% Aqueous, with actual A.I. reported as 0.5%. Batch no. 81-R-17-33.

2. Test animals: Male and female New Zealand white rabbits from Small Stock, Inc., Pea Ridge, Arkansas. Males ranged from 3.14 to 3.98 kg and females from 2.97 to 3.62 kg.

B. STUDY DESIGN:

1. Animal assignment: not stated. Five males and 5 females were treated at 2000 mg/kg. A concurrent control group (4/sex) was shaved, abraded and occluded in the same manner.

2. Test material preparation and administration: There was 24-hr occluded exposure at shaved and abraded skin sites. Animals wore collars during this period.

3. Quality assurance: under personnel and responsibilities (p. 4 of the report) the signature of R. S. Schroeder appears for Quality Assurance.

C. METHODS AND RESULTS:

1. Observations:

Rabbits were observed at least once daily for 14 days for signs of toxicity and mortality.

Toxicity:

There were no signs of toxicity.

Mortality:

There was no mortality.

2. Body weight:

Animals were weighed on days 0, 7 and 14.

Results:

Average group body weights increased (no individual body weights are reported) over the 2-week observation period.

3. Necropsies:

Survivors were sacrificed on day 14 and were examined for gross lesions.

Results:

"No gross lesions were observed at necropsy that could be related to treatment." There were no skin lesions.

D. DISCUSSION:

The study indicates a low hazard potential (toxicity category III) for this formulation in terms of its dermal toxicity (dermal LD_{50} > 2000 mg/kg).

The study is acceptable as core minimum data.

Reviewed by: Byron T. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
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DATA EVALUATION REPORT XI

STUDY TYPE: Acute dermal LD_{50} - Rabbit TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: Baygon 2% Bait

SYNONYMS: 2-(1-Methylethoxy)phenol methylcarbamate

STUDY NUMBER(S): 81-023-01

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Stanley Research Center

TITLE OF REPORT: Acute Dermal Toxicity of ®BAYGON 2% Bait

AUTHOR(S): Lamb, D. W., Hixson, E. J., English, T. D., Hoss, H. E., Mallicoat, D. R., Schroeder, R. S.

REPORT ISSUED: 04/13/81

CLASSIFICATION: Core minimum data

CONCLUSIONS:

1. This formulation has a low hazard potential (tox. category III) in terms of its dermal toxicity (no mortality or signs of toxicity at 2000 mg/kg; dermal LD_{50} > 2000 mg/kg).

A. MATERIALS:

1. Test compound: Baygon 2% Bait, with actual A.I. reported as 2.1%. Batch no. 9030074.

2. Test animals: Male and female New Zealand white rabbits from Small Stock, Inc., Pea Ridge, Arkansas. Males ranged from 2.58 to 3.08 kg and females from 2.24 to 2.50 kg.

B. STUDY DESIGN:

1. Animal assignment: not stated. Five males and 5 females were treated at 2000 mg/kg. A concurrent control group (4/sex) was shaved, abraded and occluded in the same manner. There was 24-hr occluded exposure. Animals wore collars during exposure.

2. Test material preparation and administration: "test material had been hammer-milled to a powder."

3. Quality assurance: under personnel and responsibilities (p. 4 of the report) the signature of R. S. Schroeder appears for Quality Assurance.

C. METHODS AND RESULTS:

1. Observations:

Rabbits were observed twice daily for 14 days for signs of toxicity and mortality.

Toxicity:

There were no signs of toxicity.

Mortality:

There was no mortality.

2. Body weight:

Animals were weighed on days 0, 7 and 14.

Results:

Average group body weights increased (no individual body weights are reported) over the 2-week observation period.

3. Necropsies:

Survivors were sacrificed on day 14 and were examined for gross lesions.

Results:

"No gross lesions were observed at necropsy that could be related to treatment." "Mild chronic active dermatitis was observed in treated skin or both treated and control rabbits."

4. Histopathology:

Tissue samples were taken from both treated and untreated skin. These samples were preserved in 10% buffered formalin, embedded in paraffin, sectioned at 6 um, slide-mounted, and stained with hematoxylin and eosin.

Results:

There was no "histopathologically significant cutaneous response in rabbits of either sex."

D. DISCUSSION:

The study indicates a low hazard potential (toxicity category III) for this formulation in terms of its dermal toxicity (dermal LD_{50} > 2000 mg/kg).

The study is acceptable as core minimum data.

Reviewed by: Byron C. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) 12.17.86

005692

DATA EVALUATION REPORT XII

STUDY TYPE: Acute inhalation LC_{50} - Rat TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: 0.5% Aqueous Baygon

SYNONYMS: 2-(1-Methylethoxy)phenol methylcarbamate

STUDY NUMBER(S): 81-041-12

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Stanley Research Center

TITLE OF REPORT: Acute Inhalation Toxicity Study with ®BAYGON 0.5% Aqueous in Rats

AUTHOR(S): Sangha, G. K.

REPORT ISSUED: 10/11/82

CLASSIFICATION: Core minimum data

CONCLUSIONS:

1. The study defines a low degree of hazard (tox. category III) for this formulation in terms of its inhalation toxicity (LC_{50} > 1.445 mg/l for 4 hr exposure).

A. MATERIALS:

1. Test compound: Baygon 0.5% Aqueous, a clear liquid, with A.I. reported as 0.5%. Batch no. 81-R-17-33.

2. Test animals: Young adult male and female Sprague-Dawley rats from Sasco, Inc., Omaha, Nebraska. Males ranged from 258 to 305 g and females from 196 to 241 g.

B. STUDY DESIGN:

1. Animal assignment: "animals were randomized from a table of random numbers, and groups were selected in order after randomization."

2. Test material preparation and administration: the test material was aerosolized using compressed air. A group of 10 male and 10 female rats was exposed (heads only) for 4 hrs to a nominal concentration of 5000 mg/m^3. A control group (10M, 10F) was similarly exposed to room air only.

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3. Statistical analysis: comparison of body weight means was by means of the Waller-Duncan test using a computer program.

4. Quality assurance: on p. 10 there is a statement that this report was reviewed by the Quality Assurance Unit. Also, the signature of R. S. Schroeder appears on p. 4 of this report as the individual responsible for "Analytical Chemistry and Quality Assurance."

C. METHODS AND RESULTS:

1. Exposure parameters: particle size distribution of the test material was determined three times (2, 3.5, and 3.75 hrs) using a 7-stage Cascade Impactor. The data obtained were used to calculate the mass median diameter (MMD).

The nominal concentration was calculated by dividing the weight loss of the compound sample used by the total volume of air flow through the chamber during the 4-hr exposure.

Analytical concentrations for 0.75, 1.75, 2.75 and 3.75 hrs were determined by analyzing (HPLC) Baygon content of 0.5 um Millipore filters through which 3-6 liters of chamber atmosphere had been drawn.

Results: more than 70% of the mass collected on the Cascade Impactor at each of the three times distribution was determined was less than 6.63 um. The estimated MMD was 2.1 um (average of 1.6, 2.2 and 2.6 um).

The nominal concentration of formulation was 5000 mg/m^3.

The analytical concentration was 1445 (average of 1625, 1646, 1000 and 1506) mg/m^3.

2. Observations:

Rats were observed for mortality and signs of toxicity during exposure, three times in the three hours after exposure, and then twice daily for 14 days.

Toxicity:

There were no signs of toxicity ascribable to the formulation. A non-specific irritation of the eyes and noses during exposure occurred in both exposed and control rats, and was attributed to airflow and the inability of rats to preen themselves.

Mortality:

There was no mortality.

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2. Body weight:

Animals were weighed on days 0, 2, 3, 4, 7 and 14.

Results:

Average group body weights increased (no individual body weights are reported) over the 2-week observation period.

3. Necropsies:

Survivors were sacrificed (CO_2 asphyxiation) on day 14 and were examined for gross abnormalities.

Results:

One male exposed to the formulation had dark pink lungs. None of the controls had this finding.

4. Histopathology:

Lungs, liver and kidneys were excised from each rat and were fixed in 10% buffered formalin for histopathological examination.

Results:

According to the text on p. 12 the only noteworthy finding was the presence of pulmonary alveolar macrophage foci in four exposed females and two (female) controls. According to the individual pathology tables, this finding was also present in two exposed males and 1 male control.

D. DISCUSSION:

The study defines a low degree of hazard (toxicity category III) for this formulation in terms of its inhalation toxicity (LC_{50} > 1.445 mg/l for 4 hr exposure).

The study is acceptable as core minimum data.

for 4 hrs to a nominal concentration of 508 mg/m^3. A control group (10M, 10F) was similarly exposed to room air only.

3. Statistical analysis: comparison of differences of means of body weights was done using the Waller-Duncan test on a computer program.

4. Quality assurance: there is no quality assurance statement. The signature of R. S. Schroeder appears on p. 4 of this report as the individual responsible for "Quality Assurance."

C. METHODS AND RESULTS:

1. Exposure parameters: particle size distribution was determined by sampling the chamber atmosphere with a 7-stage Cascade Impactor. The data obtained were used to calculate a mass median diameter (MMD) and geometric standard deviation.

The nominal concentration was calculated by dividing the weight loss of the compound sample used by the total volume of air flow through the chamber during the 4-hr exposure.

A gravimetric concentration was determined by drawing a sample of chamber atmosphere through a 0.5 um Millipore filter during the last hour of exposure. An additional gravimetric concentration value was obtained from the amount of material which was deposited in the Cascade Impactor (first hour of exposure).

Results: in the one run using the Cascade Impactor all particles had cut-off sizes of less than 6.6 um, and the MMD was 0.6 um. However, there was considerable similarity to particle size distribution obtained during a nonexposure period (no information is given as to the amount of material which was deposited on the Impactor during the nonexposure period).

The nominal concentration was 508 mg/m^3.

The filter sample taken the last hour of exposure showed a gravimetric concentration of 0.15 mg/m^3; the deposit on the Cascade Impactor indicated a concentration of 4.25 mg/m^3 during the first hour of exposure.

2. Observations:

Rats were observed for mortality and signs of toxicity during exposure, at 0.5, 1 and 2 hrs postexposure, and then twice daily for 14 days.

Toxicity:

All rats (exposed and control) had runny eyes during the exposure period, but appeared normal 0.5 hrs afterwards and subsequently.

Reviewed by: Byron T. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) Marcia van Gemert 12.17.86

005692

DATA EVALUATION REPORT XIII

STUDY TYPE: Acute inhalation LC_{50} - Rat TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: 2% Baygon Bait

SYNONYMS: 2-(1-Methylethoxy)phenol methylcarbamate

STUDY NUMBER(S): 81-041-01

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Stanley Research Center

TITLE OF REPORT: Acute Inhalation Toxicity of ®BAYGON 2% Bait

AUTHOR(S): Sangha, G. K.

REPORT ISSUED: 09/25/81

CLASSIFICATION: Core supplementary data

CONCLUSIONS:

1. Although a low degree of hazard for this formulation is suggested by this study (no mortalities following 4-hr exposure to a nominal concentration of 508 mg/m^3), the relatively low gravimetrically-determined concentrations of 0.15 and 4.25 mg/m^3 indicate a level of exposure insufficient to adequately classify this formulation in terms of its toxicity category.

A. MATERIALS:

1. Test compound: Baygon 2% Bait, with A.I. reported as 2%. From a description of how the dust was produced, this formulation was either granular or pelleted. Batch no. 9030074.

2. Test animals: Young adult male and female Sprague-Dawley rats from Sasco, Inc., Omaha, Nebraska. Males ranged from 218 to 249 g and females from 183 to 222 g.

B. STUDY DESIGN:

1. Animal assignment: "animals were randomized, when received, from a table of numbers. Animals for exposure were selected in order after this randomization."

2. Test material preparation and administration: dust was produced from the test material and delivered to the exposure chamber. A group of 10 male and 10 female rats was exposed (heads only)

Mortality:

There was no mortality.

2. Body weight:

Animals were weighed on days 0, 2, 3, 4, 7 and 14.

Results:

Average group body weights increased (no individual body weights are reported) over the 2-week observation period. There were no significant differences between exposed and control animals.

3. Necropsies:

Survivors were sacrificed (CO_2 asphyxiation) on day 14 and were examined for gross abnormalities.

Results:

There was lung congestion in 2 exposed male rats, a finding not reported in any of the controls.

4. Histopathology:

Lungs, liver and kidneys were excised from each rat and were fixed in 10% buffered formalin for histopathological examination.

Results:

Some (5/10) exposed males showed some degree of alveolar macrophage accumulation, but this finding was also present in 3/10 control males. There was no indication of a dose-related response involving liver and/or kidney findings.

D. DISCUSSION:

This formulation probably has a fairly low level of toxicity by the inhalation exposure route, and no mortalities occurred in this study following 4 hr exposure to a nominal atmospheric concentration of 508 mg/m^3. However, the relatively low gravimetrically-determined concentrations of 0.15 and 4.25 mg/m^3 indicate an overall exposure level insufficient to adequately classify this formulation in terms of its toxicity category (0.15 mg/m^3 = 0.00015 mg/l; toxicity category I is an LC_{50} value of 0.05 mg/l or less for 4 hr exposure).

A further complication is that the disparity (a factor of about 25) between the two gravimetrically-determined values suggests that there was considerable variation in the concentration of test material to which rats were exposed during the 4 hour run.

Reviewed by: Byron Backus 12/16/86
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D. 12/16/86
Section 3, Tox. Branch (TS-769C)

005692

DATA EVALUATION REPORT XIV

STUDY TYPE: Primary eye irritation - rabbit TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: Baygon 0.5% Aqueous

SYNONYMS: 2-(1-Methylethoxy)phenol methylcarbamate

STUDY NUMBER(S): 81-333-15

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Stanley Research Center

TITLE OF REPORT: Eye and Dermal Toxicity of ®Baygon 0.5% Aqueous

AUTHOR(S): Hixson, E. J.

REPORT ISSUED: 10/06/81

CLASSIFICATION: Core minimum data

CONCLUSIONS:

1. Conjunctival irritation (but no corneal effects or iritis) was observed in all 9 (6 unwashed, 3 washed) rabbit eyes exposed to the test material, with complete clearing by day 7. This formulation is in toxicity category III in terms of eye exposure hazard.

A. MATERIALS:

1. Test compound: Baygon 0.5% Aqueous, a clear liquid, with A.I. reported as 0.5%. Batch no. 81-R-17-33.

2. Test animals: New Zealand white rabbits, from Small Stock, Inc., Pea Ridge, Arkansas.

B. STUDY DESIGN:

1. Animal assignment: each rabbit was assigned an identification number using a table of random numbers. How the identification numbers were used is not stated.

2. Test material preparation and administration: 0.1 mls of test material was instilled in one eye of each of 9 rabbits. Three eyes were washed out at 45 seconds after instillation; the other 6 eyes remained unwashed.

3. Quality assurance: a statement is made (p. 8 of the report) that "The final report has been reviewed by the Quality Assurance Unit." Additionally, among the signatures on p. 4 is that of R. S. Schroeder, identified as responsible for quality assurance.

C. METHODS AND RESULTS:

1. Observations:

Eyes were examined on days 1, 2, 3, 4 and 7, and evaluated (scored) according to Draize.

Results:

All eyes (washed and unwashed) had some degree of erythema and chemosis and/or discharge at 1 day. There was no iritis or corneal involvement. All eyes were clear by day 7.

D. DISCUSSION:

The product is in toxicity category III (irritation clearing by day 7) in terms of eye exposure hazard. The study is acceptable as core minimum data.

Reviewed by: Byron T. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) 12/17/86

005692

DATA EVALUATION REPORT XV

STUDY TYPE: Primary dermal irritation - rabbit TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: Baygon 0.5% Aqueous

SYNONYMS: 2-(1-Methylethoxy)phenol methylcarbamate

STUDY NUMBER(S): 81-323-16

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Stanley Research Center

TITLE OF REPORT: Eye and Dermal Toxicity of ®Baygon 0.5% Aqueous

AUTHOR(S): Hixson, E. J.

REPORT ISSUED: 10/06/81

CLASSIFICATION: Core minimum data

CONCLUSIONS:

1. The product is in toxicity category IV in terms of its dermal irritation potential.

A. MATERIALS:

1. Test compound: Baygon 0.5% Aqueous, a clear liquid, with A.I. reported as 0.5%. Batch no. 81-R-17-33.

2. Test animals: New Zealand white rabbits, from Small Stock, Inc., Pea Ridge, Arkansas.

B. STUDY DESIGN:

1. Animal assignment: each rabbit was assigned an identification number using a table of random numbers. How the identification numbers were used is not stated.

2. Test material preparation and administration: 0.5 mls of test material was applied to each of 4 test sites on each of 6 rabbits, with 24-hr occluded exposure. The rabbits wore plastic collars during the exposure period.

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3. Quality assurance: a statement is made (p. 8 of the report) that "The final report has been reviewed by the Quality Assurance Unit." Additionally, among the signatures on p. 4 is that of R. S. Schroeder, identified as responsible for quality assurance.

C. METHODS AND RESULTS:

1. Observations:

Application sites were evaluated 24 and 72 hrs after application of the test material and were scored according to the method of Draize.

Results:

Slight erythema (maximum score = 1) was observed at all abraded skin sites and at a few intact sites at 24 hours. At 72 hrs all sites scored zero. PDIS = 0.31.

D. DISCUSSION:

The product is in toxicity category IV as a potential dermal irritant. The study is acceptable as core minimum data.

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Reviewed by: Byron W. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) M. van Gemert 12/17/86

DATA EVALUATION REPORT XVI

STUDY TYPE: Primary eye irritation - rabbit TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: Baygon 2% Bait

SYNONYMS: 2-(1-Methylethoxy)phenol methylcarbamate

STUDY NUMBER(S): 81-333-04

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Stanley Research Center

TITLE OF REPORT: Eye and Dermal Irritation of ®Baygon 2% Bait

AUTHOR(S): Lamb, D. W., Hixson, E. J., English, T. D., Mallicoat, D. R., Schroeder, R. S.

REPORT ISSUED: 04/13/81

CLASSIFICATION: Core minimum data

CONCLUSIONS:

1. The product is in toxicity category III (irritation clearing by day 7) in terms of eye exposure hazard. The study is acceptable as core minimum data.

A. MATERIALS:

1. Test compound: Baygon 2% Bait, a solid, with A.I. reported as 2%. Batch no. 9030074.

2. Test animals: New Zealand white rabbits, from Small Stock, Inc., Pea Ridge, Arkansas.

B. STUDY DESIGN:

1. Animal assignment: not reported.

2. Test material preparation and administration: the test material had been hammermilled to reduce individual particle size. 100 mg aliquots of this hammermilled material were instilled in one eye of each of 9 rabbits. Three eyes were washed out at 45 seconds after instillation; the other 6 eyes remained unwashed.

3. Quality assurance: Among the signatures on p. 4 is that of R. S. Schroeder, identified as responsible for quality assurance.

C. METHODS AND RESULTS:

1. Observations:

Eyes were examined on days 1, 2, 3, 4 and 7, and evaluated (scored) according to Draize.

Results:

All eyes (washed and unwashed) had some degree of erythema. All unwashed eyes also had some chemosis and discharge, as did 2/3 washed eyes. There was no iritis or corneal involve- in any eye. All eyes were clear by day 7.

D. DISCUSSION:

The product is in toxicity category III (irritation clearing by day 7) in terms of eye exposure hazard. The study is acceptable as core minimum data.

Reviewed by: Byron [redacted]. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) Marcia van Gemert 12.1.81

005692

DATA EVALUATION REPORT XVII

STUDY TYPE: Primary dermal irritation - rabbit TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: Baygon 2% Bait

SYNONYMS: 2-(1-Methylethoxy)phenol methylcarbamate

STUDY NUMBER(S): 81-323-04

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Stanley Research Center

TITLE OF REPORT: Eye and Dermal Irritation of ®Baygon 2% Bait

AUTHOR(S): Lamb, D. W., Hixson, E. J., English, T. D., Mallicoat, D. R., Schroeder, R. S.

REPORT ISSUED: 04/13/81

CLASSIFICATION: Core minimum data

CONCLUSIONS:

1. The product is in toxicity category IV in terms of its dermal irritation potential.

A. MATERIALS:

1. Test compound: Baygon 2% Bait, a solid, with A.I. reported as 2%. Batch no. 9030074.

2. Test animals: New Zealand white rabbits, from Small Stock, Inc., Pea Ridge, Arkansas.

B. STUDY DESIGN:

1. Animal assignment: not reported.

2. Test material preparation and administration: 0.5 mls of hammermilled test material, moistened with physiological saline, was applied to each of 4 (2 intact, 2 abraded) test sites on each of 6 rabbits, with 24-hr occluded exposure. Rabbits wore plastic collars during the exposure period.

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3. Quality assurance: Among the signatures on p. 4 is that of R. S. Schroeder, identified as responsible for quality assurance.

C. METHODS AND RESULTS:

1. Observations:

Application sites were evaluated 24 and 72 hrs after application of the test material and were scored according to the method of Draize.

Results:

Slight erythema (score = 1) was observed at 3 abraded skin sites at 24 hours. All other sites scored zero. At 72 hrs all sites scored zero. PDIS is reported as 0.00 (actually should be 0.06).

D. DISCUSSION:

The product is in toxicity category IV as a potential dermal irritant. The study is acceptable as core minimum data.

Reviewed by: Byron T. Backus
Section 3, Tox. Branch (TS-769C)

005692

Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) M van Gemert 12.17 86

DATA EVALUATION REPORT XVIII

STUDY TYPE: human exposure - mosquito control use

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: Baytex 97% LC

SYNONYMS: 2-(1-Methylethoxy)phenol methylcarbamate

STUDY NUMBER(S): 53115

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: n/a

TITLE OF REPORT: n/a

AUTHOR(S): n/a

REPORT ISSUED: February-March 1976

CLASSIFICATION: Core supplementary data

CONCLUSIONS:

1. The toxicological value of this submission is extremely limited, as no data are provided as to actual levels of Baygon to which human exposure occurred. Also, no attempts were made to determine plasma and/or RBC ChE levels before and after exposure, or even to determine if there was measurable 2-Isopropoxyphenol (a metabolite of Baygon) in the urine.

A. MATERIALS:

Test compound: BAYTEX 93% LC

B. BACKGROUND:

This submission consists of a number of reports (testimonials would be a better word) as to the lack of noticeable toxic effects in applicators who sprayed the product at normal use levels (0.5-2 oz/acre) for mosquito control. Applicator exposure included that involved in pouring the chemical in a machine, during which time protective clothing was ostensibly worn, and some incidental exposure to drift. Additionally, there was some exposure (to fogs and/or drift) involving local human populations.

C. FINDINGS:

There were no noticeable toxic effects in applicators who had an exposure to this formulation associated with loading and getting some drift from the spray, nor were any reported from other humans who were exposed to the spray or drift.

D. DISCUSSION:

The toxicological value of this report is extremely limited, as no information is provided as to actual levels of the active to which human exposure occurred. Additionally, no attempts were made to determine plasma and/or RBC ChE levels following exposure, or even to determine if there was measurable 2-Isopropoxyphenol (a metabolite of Baygon) in the urine.

Reviewed by: Byron T. Backus
Section 3, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) MvanGemert 12.17.86

005692

DATA EVALUATION REPORT XIX

STUDY TYPE: 5-day oral dosing & enzyme induction - rat

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: Carbamate UN, Technical (98.6% Propoxur)
Carbamate UN, recrystallized (99.2% Propoxur)

SYNONYMS: Propoxur, Baygon,

STUDY NUMBER(S): 11621

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Carbamate UN, Technical, Subacute Study on Rats, Compared with Carbamate UN, Recrystallized

AUTHOR(S): Heimann, K.-G.

REPORT ISSUED: 03/08/83

CLASSIFICATION: core supplementary data

CONCLUSIONS:

1. There was no evidence of induction of some liver enzyme activities (N-demethylase, O-demethylase, cytochrome P-450) in rats as a result of their being orally dosed at 15 and 30 mg/kg/day (levels at which there were symptoms of toxicity, but no mortality) over a 5-day period. Also, there was no evidence of effects involving liver triglyceride level.

2. There was no evidence of effects involving a limited number of blood clinical chemistry parameters (SGOT, SGPT, ALP, urea, glucose, creatinine or bilirubin).

3. There was no indication of effects involving absolute organ weights or body-to-organ weight ratios for liver and kidneys.

4. There was no indication of any toxicological difference between Carbamate UN technical (98.6% active) and Carbamate UN recrystallized (99.2% active).

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A. MATERIALS:

1. Test compounds:

Carbamate UN, technical. No description. Mixed batch #55199; purity 98.6%.

Carbamate UN, technical, recrystallized. No description. Mixed batch no. 131588; purity 99.2%

2. Test animals: Species: rat, Strain: Wistar albino WISW (SPF-CPB), Age: not given, Weight: 140-170 g., Source: Winkelmann in Borchen, Kreis Paderborn.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Material received	Daily dose (mg/kg)	No. of rats male	female
IA	vehicle (PEG 400)	-	5	5
IB	vehicle (PEG 400)	-	5	5
II	Carbamate UN	15	5	5
III	Carbamate UN	30	5	5
IV	Carbamate UN, recryst.	15	5	5
V	Carbamate UN, recryst.	30	5	5

This reviewer has interpreted the data presentation as indicating there were 2 separate control groups, each with 5 males and 5 females; comparison of the findings for "carbamate UN" was with one of these control groups, and comparison of the findings for "carbamate UN, recrystallized" was with the other.

2. Dose preparation

Test samples were formulated in polyethylene glycol 400 (PEG 400) so that a uniform dose volume of 5 ml/kg body weight was received by each animal. Rats were dosed once daily on 5 consecutive days using a stomach tube.

3. Animals received food ("Altromin R feed for rats and mice") and water ad libitum.

4. Statistics - Means of a number of parameters were analyzed, and whether or not they were significantly different at p = 0.05 and/or 0.01 is reported. However, there is no indication as to how calculations were made (possibly Student T-test?).

5. Quality assurance: There is no quality assurance statement.

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C. METHODS AND RESULTS:

1. Observations: animals were observed daily for behavior and appearance.

   The two test materials are reported (p. 2) as producing "cholinergic symptoms in both the doses tested; they were however tolerated without somatic damage." According to the text on p. 7 symptoms included slight convulsions and apathy lasting 1-3 hrs (after dosage?).

   There was no mortality.

2. Body weight: animals were weighed daily.

   Results: there were no significant differences between dose group means and controls.

3. Food consumption: there are no food consumption data.

4. Ophthalmalogical examinations: there were no ophthalmalogical examinations.

5. Blood was collected by cardiac puncture after rats were sacrificed by diethyl ether narcosis (day 5). The CHECKED (X) parameters were examined.

   a. Hematology (no hematology measurements were made).

   b. Clinical Chemistry

	Electrolytes:		Other:
	Calcium*		Albumin*
	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
	Phosphorous*		Cholesterol*
	Potassium*		Globulins
	Sodium*	X	Glucose*
	Enzymes	X	Bilirubin*
X	Alkaline phosphatase		Total Serum Protein*
	Cholinesterase#		Triglycerides
	Creatinine phosphokinase*°		Serum protein electrophoresis
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

* Required for subchronic and chronic studies
° Not required for subchronic studies # Should be required for OP

Results:

Carbamate UN:

The only significant difference involved blood sugar levels in 30 mg/kg/day females and their respective controls. Males at this dose level also showed an elevated level with respect to their controls. From p. 11 (also given on p. 42):

Group	Glucose (mmol/l)
Control males	5.46
Males 15 mg/kg/day	6.08
Males 30 mg/kg/day	6.28
Control females	5.29
Females 15 mg/kg/day	5.97
Females 30 mg/kg/day	6.04*

*Reported as significantly different from control value at $p < 0.05$.

According to the text on p. 8: "The statistically slightly significant increase in blood sugar level for the female animals in the highest dose group...is unimportant, as the deviation was only very slight and the reading was within the physiological norm."

Carbamate UN recrystallized:

The following significant (and possibly dose-related) differences occurred for at least one sex; from p. 12:

Group	Urea mmol/l	Creatinine mcmol/l	Bilirubin mcmol/l	ALP u/l
Control males	5.57	48	1.9	469
Males 15 mg/kg/day	4.72	46	2.1	515
Males 30 mg/kg/day	4.33*	41**	3.3*	543
Control females	5.69	57	3.2	186
Females 15 mg/kg/day	5.54	50	2.7	255*
Females 30 mg/kg/day	5.04	47*	3.0	274**

*Reported as significantly different from control value at $p < 0.05$.
**Reported as significantly different from control value at $p < 0.01$.

On p. 8 a statement is made that the dose-related and decrease in urea and creatinine was "not toxicologically relevant, as only an increase would be significant."

The increased mean bilirubin in 30 mg/day males is stated to be: "biologically unimportant, as the effect was very slight and the value was entirely within the normal range."

The statistically significant increased alkaline phosphatase (ALP) activity in females is reported to be a result of the control mean being low.

6. Liver homogenates were prepared after sacrifice, and the following examinations were made:

Enzyme activities:

N-demethylase
O-demethylase
cytochrome P-450

Other:

triglyceride extraction

Results:

From p. 8: "examination of the microsomal liver enzyme activities and of the triglycerides did not reveal any significant deviations compared with the control or normal range, either...with Carbamate UN...or...Carbamate UN, recrystallised."

Individual values are given on p. 54-55 (Carbamate UN) and p. 61-62 (Carbamate UN recrystallized). Examination of these data and corresponding means (p. 56 and p. 63) indicate there were no evident effects on these parameters as a result of dosage with either (or both) Carbamate UN or Carbamate UN recrystallized at 15 or 30 mg/kg/day for 5 days.

7. Urinalysis was not done.

8. Pathology and Organ Weights:

Rats were sacrificed (exsanguination by heart puncture under ether narcosis) about 24 hours after the fifth and last dosage of the test material. They were then dissected and examined for pathological changes, followed by removal and weighing of livers and kidneys.

Results:

The statement is made (p. 15) that: "no macroscopic alterations were noted which were induced by treatment or deviated from the norm." However, the submission does not include any individual (or even group) pathology findings.

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There only significant difference between organ weights involved a mean liver-to-body-weight increase for males dosed with Carbamate UN recrystallized at 30 mg/kg/day and their respective controls. From p. 92:

	Mean relative organ-to-body weight ratio (mg/100 g)
Control males	4378
Males - 15 mg/kg/day Carbamate UN recryst.	4293
Males - 30 mg/kg/day Carbamate UN recryst.	4685*

*significantly ($p < 0.05$) different from control value.

This was due to the value obtained from a single male (#44, see p. 75 & 89).

Interestingly, males dosed with Carbamate UN (not recrystallized) at 30 mg/kg/day had a somewhat lower (not significantly so) mean liver-to-body weight ratio than their controls. From p. 84:

	Mean relative organ-to-body weight ratio (mg/100 g)
Control males	4625
Males - 15 mg/kg/day Carbamate UN	4654
Males - 30 mg/kg/day Carbamate UN	4371

D. DISCUSSION:

The major finding is that there was no evidence of induction of some liver enzyme activities (N-demethylase, O-demethylase, cytochrome P-450) in rats as a result of their being orally dosed at 15 and 30 mg/kg/day over a period of 5 days. Also, there was no evidence of effects on triglyceride level in the liver.

There was also no evidence of effects involving a limited number of blood clinical chemistry parameters, and absolute (along with relative organ-to-body weight ratios) for the liver and kidney.

The study is classified as core supplementary.

Reviewed by: Byron T. Backus
Section 3, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) M. van Gemert 12.17.86

005692

DATA EVALUATION REPORT XX

STUDY TYPE: 12-month feeding, dog

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: BOE 58 123 15, c.n. Propoxur

SYNONYMS: 2-isopropoxyphenyl-N-methylcarbamate

STUDY NUMBER(S): 12605

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Chronic Toxicity to Dogs on Oral Administration

AUTHOR(S): Hoffmann, K. and Gröning, P.

REPORT ISSUED: 04/11/84

CLASSIFICATION: core supplementary data

CONCLUSIONS:

1. A NOEL was not observed in this study, as the low dose (200 ppm) group showed statistically significant elevations for mean plasma cholesterol at 13, 26 and 52 weeks relative to controls, and these findings were part of dose-related trends.

2. At 600 ppm there were statistically significant increases in mean liver weight and mean N-demethylase activity, along with increased plasma cholesterol. Males (but not females) showed a lower (about 25%) mean weight gain than did their controls (2.92 to 3.89 kg), although this was not statistically significant ($p = 0.1543$ by paired T-test). Also, thymus weights were somewhat lower than normal in 2/6 males. During the first week (but not subsequently) RBC ChE activity was significantly lowered one hour after feeding, but had recovered at 24 hours.

3. The high-dose dogs were dosed at 1800 ppm through week 40, 3600 ppm for weeks 41-44, then 5400 ppm for weeks 45-52. A major problem in attempting to interpret the findings from this group is that in addition to long-term (1-year) exposure to Propoxur at 1800 ppm and above, the dogs were stressed during the final weeks, as symptoms of cholinesterase inhibition were present after the dosage level was raised to 5400 ppm.

4. Besides findings present in lower dose groups (significant increases in mean liver weight, plasma cholesterol level, N-demethyase activity), mean weight gains were depressed by about 30% in males (not statistically significant with p = 0.0832) and by about 15% in females relative to their respective controls at week 40. After week 40 high-dose dogs tended to lose weight and the mean weights for the group became significantly lower than those of controls. Mean thrombocyte counts were consistently and significantly increased throughout the study. Mean serum protein was significantly lower than that of controls at weeks 6, 26, 39, 43, 48 and 52, and this was primarily due to a lower albumin level. Mean GPT activity was significantly elevated at weeks 48 and 52, and there was also increased AP activity at weeks 43, 48 and 52. Plasma ChE was depressed (about 25%) relative to control levels, but RBC ChE was significantly depressed only at 1 hour after feeding during the first week. At termination, mean thymus weight was significantly lower than that of controls, and this was associated with a 100% incidence of atrophy. The lower mean spleen weight was probably related to the reduced thymus weight.

5. Increases in mean adrenal and kidney weights in high-dose dogs, as well as the mortality in one during week 50, may have been related to stress during weeks 45-52 when the dose level was 5400 ppm and symptoms of cholinesterase inhibition were evident.

6. No histopathology findings are reported from 200 or 600 ppm dogs, despite a 100% incidence of atrophy of the thymus in high-dose dogs and a reduced (but not significantly so) mean thymus weight for 600 ppm males.

A. MATERIALS:

1. Test compound: BOE 58 123 15, Description not given, made from batches 234001222 to 234001226, purity 99.4%, stored dry at room temperature.

2. Test animals: Species: dog, Strain: thoroughbred beagle, Age: 15-24 weeks old, Weight: 5.0-8.0 kg, Source: F. Winkelmann, D-4799 Borchen, West Germany.

B. STUDY DESIGN:

1. Animal assignment
After sorting by sex and weight, dogs were assigned by "randomization" to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 12 months male	female	Interim Sac. male	female
1 Controls	0	6	6	no interim sac.	
2 Low (LDT)	200	6	6	no interim sac.	
3 Mid (MDT)	600	6	6	no interim sac.	
4 High(HDT)	1800*	6	6	no interim sac.	

*1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.

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2. Diet preparation

A pulverized dry feed ("Ssniff-HH Sole Diet") was used. Mixtures containing the test compound were prepared weekly; according to the text on p. 240* the mixture was stored at room temperature (at least for stability studies). Diet was mixed (1:1) with water just before being given to the dogs. Samples of treated food were analyzed for stability and concentration at weeks -1, 17, 26, 39 and 52.

Results:

Recoveries (p. 239), expressed in terms of % of theoretical, ranged from 87% to 108%. Recovery at 10-11 days ranged from 88-96% in one sampling from each of 4 different concentrations. The compound was also shown to be stable for 24 hrs in the diet as given (1:1 mixture with water) to the dogs.

3. Animals received food (individual amounts: 250 g/day through week 7; 280 g/day through week 12, 300 g/day through week 27; 330 g/day through week 40; 350 g/day through week 50; and 400 g/day through week 52) and water ad libitum. From examination of the data the weights given above are for the dry food (rather than the 1:1 mixture with water).

4. Statistics - From p. 17: "Notable differences between the control figures and those of the animals treated with the test compound were checked for statistical significance with Wilcoxon's non-parametric rank sum test."

5. Quality assurance: There is no quality assurance statement.

C. METHODS AND RESULTS:

1. Observations

a. General: Animals were inspected several times daily for signs of toxicity and mortality.

Toxicity:

The overall incidence of vomiting is reported as "very slight" in all groups through week 40. At week 41 the dietary concentration of test material was raised from 1800 to 3600 ppm in

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*There are 3 numbers on each page of this study. In this review the number used will be that appearing on the bottom middle of each page.

Results:

From p. 19: "reflex tests...did not detect any abnormal reactions in any of the animals throughout the treatment." There were no indications of any treatment-induced effects involving body temperatures and/or pulse rates.

2. Body weight

Animals were weighed weekly during the entire study.

Results: The following are from mean body weights at the weeks indicated (from data on p. 95-98):

Group	Dose	Mean weight (kg) at week:						
Males	(ppm)	start	10	20	30	40	45	50	52
1 Controls	0	6.58	7.85	9.00	9.45	9.93	10.18	10.22	10.47
2 Low (LDT)	200	6.60	7.88	9.13	9.72	10.23	10.53	10.50	10.72
3 Mid (MDT)	600	6.48	7.23	8.25	8.72	9.03	9.18	9.22	9.40
4 High(HDT)	1800†	6.50	7.25	7.98	8.37	8.83	8.62	8.12	7.96*
Females	(ppm)	start	10	20	30	40	45	50	52
1 Controls	0	6.55	7.68	8.55	8.97	9.50	9.68	9.67	9.85
2 Low (LDT)	200	6.23	7.50	8.68	9.27	9.90	10.00	10.17	10.48
3 Mid (MDT)	600	6.15	7.12	8.25	8.78	9.30	9.50	9.50	9.50
4 High(HDT)	1800†	6.22	7.32	8.07	8.40	8.73	8.58	8.05	8.23*
4.High(HDT)	1800†°	6.34	7.50	8.46	8.84	9.16	9.04	8.46	8.68

†1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.
*$p \leq 0.01$ (compared with controls)
°without data from K688 (see below)

At week 41 and thereafter mean body weights for all dogs (combined males and females) in the high-dose group were significantly lower than controls (wk 41-44, $p \leq 0.05$; wk 45, $p \leq 0.02$; wk 46-52, $p \leq 0.01$).

Both males and females at 200 ppm had slightly greater (but probably not significantly so) mean weight gains than their respective controls; females at 600 ppm had weight gains similar to their controls. High-dose males and females, as well as 600 ppm males, had lower mean weight gains. One high-dose female (K688) had poor weight gain (1.3 kg) in the first 40 weeks. However, even when means are recalculated excluding this dog high-dose females had less mean weight gain than any other group.

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Weight gains (statistical significance not calculated):

Males Group	Dose (ppm)	Mean weight gain (kg) by week: 10	20	30	40	45	50	52
1 Controls	0	1.27	2.42	2.87	3.35	3.60	3.64	3.89
2 Low (LDT)	200	1.28	2.53	3.12	3.63	3.93	3.90	4.12
3 Mid (MDT)	600	0.75	1.77	2.24	2.55	2.70	2.74	2.92
4 High(HDT)	1800†	0.75	1.48	1.87	2.33	2.12	1.62	1.58¶
Females	(ppm)	10	20	30	40	45	50	52
1 Controls	0	1.13	2.00	2.42	2.95	3.13	3.12	3.34
2 Low (LDT)	200	1.27	2.45	3.04	3.67	3.77	3.94	4.25
3 Mid (MDT)	600	0.97	2.10	2.63	3.15	3.35	3.35	3.35
4 High(HDT)	1800†	1.10	1.85	2.18	2.51	2.36	1.83	2.01
4 High(HDT)	1800†,°	1.16	2.12	2.50	2.82	2.70	2.12	2.34

†1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.
¶One dog died week 50.
°Without data from K688.

Female K688 in the high-dose group "appeared emaciated at the end of the study" (p. 20). This dog was one of those vomiting more frequently after week 41; and had gone from 6.6 kg at week 40 to 6.0 kg at week 52. While other dogs in the high-dose group showed similar weight losses during this period, K688's weight at week 40 was lowest of any dog in the study (and had been so since week 9).

3. Food consumption and compound intake

Consumption was determined and mean daily diet consumption was calculated.

Results:

From p. 22: "Most...dogs consumed the food offered to them almost completely during the entire study period. Only towards the end of the twelve months of treatment - after increase of the daily food ration to 350 g (week 41) and 400 g (week 51) per animal - individual females in particular repeatedly left food. Although this effect was observed in all the groups, the group III animals' average food consumption was less than that of the other groups from about week 43..."

After week 32, dog K688, previously noted as weighing the least of any female in the study, frequently (weeks 32, 34-35, 37-46, 49, 51-52) did not consume the entire amount of food offered (however, it had weighed the least since week 9, despite consuming all the food offered through week 31).

Food efficiency was not calculated. However, mean weight

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gains for high-dose animals were below those of other groups for the first 40 weeks (even without including data from K688), despite equivalent food consumptions.

The mean quantities of propoxur consumed per animal per group are reported on p. 22 & 26 as the following:

Test Group	Dose in diet (ppm)	Mean quantity of propoxur consumed per animal	
		Total	Per week
1 Controls	0	-	-
2 Low (LDT)	200	22.71 g	437 mg
3 Mid (MDT)	600	67.82 g	1304 mg
4 High(HDT)	1800†	284.19 g	5465 mg

†1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.

4. Ophthalmalogical examinations

All eyes were examined at weeks -2, 6, 12, 26, 39 and 52 with a Heine® ophthalmoscope. The eye fundus was photographed before the start of the study and again at the final examination.

Results:

According to the text on p. 30-31 there were no group specific findings in the cornea, anterior chamber, lens, vitreous body or in the eye fundus. There were no indications of any vision impairment in any of the dogs.

5. Blood was collected at weeks -2, 6, 13, 26, 39 and 52 from all dogs. Also, blood was collected from controls and high-dose dogs only at weeks 43 and 48. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet (thrombocyte) count*	X	Reticulocyte count
	Blood Clotting Measurements	X	Blood corpuscle sedimentation rate
X	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

high-dose dogs, after which 3 of the dogs in this group showed an increased incidence of vomiting. 005692

No other symptoms were noted until the dietary concentration of test material being fed to high-dose dogs was again raised (this time to 5400 ppm) at week 45. After this there was an increased incidence of vomiting in almost all the dogs in this group; some of these dogs also showed more frequent salivation. Additionally, most

dogs in this group showed spasms throughout their entire bodies after feeding, while two "exhibited an uncertain gait with slightly bent joints." One dog "temporarily showed aggressive behaviour" and another "exhibited circular movements."

On p. 20 it is stated that feces were of normal consistency at doses up to and including 5400 ppm of test material.

Blood in feces, attributed to parasites, occurred in two high-dose dogs (once in each case), but no information appears to be present in this report as to when these observations were made. On p. 21 it is stated that all dogs were wormed in weeks 2, 5, 30 and 34 with 20% Uvilon® syrup at 1.1 ml/kg b.w.

Mortality (survival)

One high-dose dog (K679) was found dead at week 50. This dog was the only one in this group which had shown no clinical symptoms up to this time. The text states there was no evidence of injuries or illness (although this dog had earlier been one of two showing "slight quantities" of blood in the feces). Examination of individual food consumption data (see p. 66) indicates that while almost all high-dose males had a food consumption drop for weeks 48 and 49, that of K679 had dropped the most. This dog also had a considerable weight loss (from 8.2 kg to 7.4 kg; see p. 90) between 48 and 49 weeks, but it was back to 7.9 kg at week 50.

b. Physical examinations:

From p. 12: "reflex tests (pupil reaction, corneal reflex, patellar tendon reflex, and stretch, righting and bending reflex) took place for all the animals" at weeks -1, 6, 13, 26, 39 and 52. Body temperatures and pulse rates were also measured at these times.

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Results:

Mean thrombocyte counts were consistently (and significantly) elevated in high-dose dogs; and there was an additional increase in this parameter in these dogs after week 40 (when the test material concentration was increased); from p. 32:

Thrombocyte counts $10^9/l$

Test Group	Dose in diet (ppm)	week -2	6	13	26	39	43	48	52
1 Controls	0	310.6	271.3	267.9	239.5	228.7	271.1	269.8	283.3
2 Low (LDT)	200	311.7	280.0	277.5	243.8	247.8	-	-	295.7
3 Mid (MDT)	600	306.1	298.0	309.4	250.8	236.1	-	-	307.5
4 High(HDT)	1800†	324.9	359.1*	341.2*	324.3*	295.6*	349.7*	359.1*	456.6*

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.
* $p \leq 0.01$

Examination of individual data for the high-dose group (p. 105-106) shows that all dogs had elevated thrombocyte counts, and there was no evident sex-related difference (mean for high-dose males at 52 weeks: 438.2 x $10^9/l$; for females: 472 x $10^9/l$; comparable values for controls: 280.5 x $10^9/l$ and 286 x $10^9/l$).

No consistent dose-related differences were observed for any of the other hematology parameters.

b. Clinical Chemistry

The CHECKED (X) parameters were examined.

X	Electrolytes:	X	Other:
X	Calcium*		Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
	Phosphorous*	X	Cholesterol*
X	Potassium*		Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total Bilirubin*
X	Alkaline phosphatase	X	Total Serum Protein*
	Creatinine phosphokinase*°		Triglycerides
	Lactic acid dehydrogenase	X	Serum protein electrophoresis
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	gamma glutamyl transferase		
X	glutamate dehydrogenase		

° Not required for subchronic studies
* Required for subchronic and chronic studies

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In addition, the following enzyme assays were done following sacrifice using liver tissue:

N-demethylase
Cytochrome P-450

Results:

Both mid and high-dose dogs usually had significantly increased mean cholesterol levels, and, from examination of the data on p. 37, even the low-dose dogs tended to be elevated in this respect. As reported on p. 37:

Mean cholesterol levels MMOL/l

Test Group	Dose in diet (ppm)	week -2	6	13	26	39	43	48	52
1 Controls	0	2.531	2.930	3.424	2.877	4.046	3.427	3.354	2.928
2 Low	200	2.495	3.487	4.132	3.822	4.277	-	-	3.563
3 Mid	600	2.556	3.667[a]	4.534[c]	3.995[c]	4.827[a]	-	-	3.980[c]
4 High	1800†	2.567	4.134[b]	4.830[c]	4.098[c]	4.851[a]	4.609	4.561[c]	4.205[c]

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.
[a]$p \leq 0.05$, [b]$p \leq 0.02$, [c]$p \leq 0.01$

It is noteworthy that there is no indication on p. 37 that any of the mean cholesterol levels in the 200 ppm group were statistically significantly different from those of controls for the same date. Using two sample T-tests the following values for p were calculated between test groups and their controls (variances assumed to be unequal, which leads to a slightly higher value for p than if variances are equal):

p-values from t-test comparison with control values:

Test Group	Dose in diet (ppm)	week 6	13	26	39	52
2 Low	200	0.0743	0.0271	0.0038	0.5265	0.0406
3 Mid	600	0.0137	0.0003	0.0019	0.0477	0.0045
4 High	1800†	0.0005	0.0033	0.0010	0.0406	0.0010

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.

The above indicates that the mean serum cholesterol levels in 200 ppm dogs were significantly ($p \leq 0.05$) different from control means at 13, 26 and 52 weeks, and approached ($p = 0.0743$) statistical significance at week 6. There was no statistically significant difference at week 39 when the control mean was somewhat higher than usual. Somewhat similar results were obtained using Wilcoxon's Signed Rank Test (i.e., for week 13 the one-tailed P value is 0.0261, for week 26 it is 0.0024, for week 52 it is 0.0212).

Serum protein was usually significantly lower in high-dose dogs; from p. 37:

Serum protein g/l

Test Group	Dose in diet (ppm)	week -2	6	13	26	39	43	48	52
1 Controls	0	51.97	54.19	55.29	57.60	58.58	61.09	60.29	56.58
2 Low	200	51.92	52.23	54.73	56.79	57.76	-	-	56.01
3 Mid	600	53.08	52.71	55.44	56.46	56.75	-	-	58.07
4 High	1800†	53.35	50.80[b]	52.76	54.14[c]	54.73[c]	51.79[c]	51.37[c]	50.97[c]

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.
[a]$p \leq 0.05$, [b]$p \leq 0.02$, [c]$p \leq 0.01$

Lower mean serum protein levels in high dose animals were due largely to a statistically lower (from week 43) albumin level, as for example at week 52 (calculated from data on p. 42):

Serum protein g/l

Test Group	Dose (ppm)	Serum protein g/l	% albumin	serum albumin g/l	serum non-albumin g/l
1 Controls	0	56.58	57.17	32.35	24.23
2 Low	200	56.01	55.13	30.88	25.13
3 Mid	600	58.07	56.27	32.68	25.39
4 High	1800†	50.97	53.62[b]	27.33[d]	23.64[d]

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 540
[a]$p \leq 0.05$, [b]$p \leq 0.02$, [c]$p \leq 0.01$, [d] p not calculated

Mean GPT activity tended to be higher in 600 ppm and high-dose dogs (not necessarily in a dose-related fashion), but was significantly higher only for high-dose dogs at 48 and 52 weeks.

GPT u/l

Test Group	Dose in diet (ppm)	week -2	6	13	26	39	43	48	52
1 Controls	0	19.56	22.29	21.39	24.07	24.18	25.08	21.59	23.28
2 Low	200	20.90	22.90	22.03	25.27	22.24	-	-	26.70
3 Mid	600	20.56	26.25	27.78	32.16	24.07	-	-	26.38
4 High	1800†	19.81	32.56	23.18	27.07	27.29	32.09	34.14[c]	40.45[a]

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.
[a]$p \leq 0.05$, [b]$p \leq 0.02$, [c]$p \leq 0.01$

The high value at week 6 for the 1800 ppm group was due to K688, as otherwise the mean GPT activity was 23.91 u/l. At 52 weeks the increase in GPT activity was not evenly distributed among all high-dose dogs, as three (K677, K688, K665) had a mean of 76.63 u/l, while the remaining 8 had 26.89 u/l. However, even among these 8 this value was a rise in mean GPT from that at week 39 (19.23 u/l).

Mean alkaline phosphatase (AP) activity tended to be higher in all groups receiving the test compound, but was signifi-

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cantly so only in high-dose dogs after week 39:

AP u/l

Test Group	Dose in diet (ppm)	week -2	6	13	26	39	43	48	52
1 Controls	0	231.1	164.0	155.0	133.8	152.5	124.1	123.7	138.3
2 Low	200	281.8	226.3	222.2	206.5	193.2	-	-	251.8
3 Mid	600	276.6	214.8	208.9	178.8	175.3	-	-	204.8
4 High	1800†	265.6	213.9	216.8	208.9	219.7	275.8[b]	249.4[b]	270.2[c]

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.
[a]$p \leq 0.05$, [b]$p \leq 0.02$, [c]$p \leq 0.01$

Mean AP activity at week 39 for high-dose dogs was elevated (but not significantly) with respect to controls, but this was due to an extremely high value (855 u/l) from dog K688. Mean AP activity from the eleven remaining dogs was 161.9 u/l. At week 52 the level for K688 was 633 u/l, with the other dogs having a mean of 233.9 u/l, a value below that of the 200 ppm dogs.

Given the means for AP activity at 52 weeks, it is surprising that the 200 ppm value (251.8 u/l) is not reported as significantly different from that of controls (138.3 u/l), particularly as 270.2 (the mean for high-dose dogs) is reported as significantly different from the control value at $p \leq 0.01$ (p. 37).

At termination mean N-demethylase activity was significantly elevated in mid-dose and high-dose dogs; cytochrome P450 was elevated (not significantly) in high-dose dogs only; from p. 38:

Test Group	Dose in diet (ppm)	N-demethylase activity at term.	P-450 activity at termination
1 Controls	0	62.058	21.192
2 Low	200	68.875	19.375
3 Mid	600	80.017[c]	20.958
4 High	1800†	122.336[c]	25.036

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.
[a]$p \leq 0.05$, [b]$p \leq 0.02$, [c]$p \leq 0.01$

c. Cholinesterase (ChE) activity:

Plasma and RBC ChE were determined for all dogs during weeks -1 (twice), 1, 3, 6, 13, 26, 39 and 52 (and apparently at 0, 1 and 24 hours at each of these times). Additional determinations were made on all high-dose dogs and controls in weeks 41, 43 and 46, and for high-dose dogs only in week 45. Brain (bulbus olfactorius) ChE was determined following sacrifice.

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Results:

According to the text on p. 43, plasma ChE activities taken 1 hour after administration (daily feeding?) were reduced by 20-25% in high-dose dogs relative to controls up to week 46, and by about 35% in week 52. Also according to the text (p. 44) RBC ChE activity was reduced in high-dose dogs 1 hour "after administration" of the test compound only for treatment week 1. There was no effect on brain ChE (taken at termination), and plasma ChE inhibition was not observed at 200 or 600 ppm.

Examination of the means for plasma ChE activities in high-dose dogs (see p. 202-205) does not support the statement (p. 44) that (plasma) ChE activities returned to normal in this group within 24 hours. For example, at weeks 13, 26 and 39 the mean plasma activities for 0, 1 and 24 hours are given as the following for controls and high-dose dogs (from p. 203-204):

Plasma ChE

Test Group	Dose in diet (ppm)	week								
		13			26			39		
		0 hr	1 hr	24 hr	0 hr	1 hr	24 hr	0 hr	1 hr	24 hr
1 Controls	0	1.671	1.698	1.580	1.921	1.916	1.777	1.771	1.812	1.857
4 High	1800†	1.427	1.337	1.334	1.552	1.558	1.474	1.522	1.469	1.507

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.

These data indicate that there was a continual plasma ChE depression in high-dose dogs.

From individual data (p. 195-200) it is noteworthy that K688 (the dog with some of the most pronounced effects) usually had the lowest plasma ChE activity in the high-dose group.

Examination of group RBC ChE activities at one week for 0, 1 and 24 hours using two-sample T tests indicates the following:

At 1 hour, there was a significant difference ($p = 0.0001$) between the control mean (2.438 KU/L) and that of the 1800 ppm group (1.952 KU/L). At 0 hours, there was no significant difference between the control mean (2.390 KU/L) and that of the 1800 ppm group (2.391 KU/L). Again, at 24 hrs there was no significant difference between the control mean (2.501 KU/L) and that of the 1800 ppm group (2.508 KU/L). There were significant differences between the 0 hr mean for the 1800 ppm group and that of the same group at 1 hr (2.391 and 1.952 KU/L respectively, with $p = 0.0001$) and the 1800 ppm mean at 24 hrs and that at 1 hr (2.508 and 1.952 KU/L respectively, with $p = 0.0000$).

While the difference between the 1 hr control and 600 ppm group RBC ChE means was not significant (2.438 and 2.268 KU/L respectively, with $p = 0.0983$), the differences between the 600 ppm group means for 0 and 1 hr (2.587 and 2.268 KU/L, with $p = 0.0028$) and for 24 and 1 hr (2.707 and 2.268 KU/L, with $p = 0.0001$) were.

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6. Urinalysis°

Urine was collected at -1, 6, 13, 26, 39 and 52 weeks. Additional determinations were made for controls and high-dose dogs at weeks 41, 43 and 46. The CHECKED (X) parameters were examined.

X		X		X	
	Appearance*	X	Sediment (microscopic)*	X	Bilirubin*
X	Volume*	X	Protein*	X	Blood*
X	Specific gravity*	X	Glucose*		Nitrate
X	pH	X	Ketone bodies*		Urobilinogen

* Required for chronic studies
° Not required for subchronic studies

Results:

The text states (p. 44-45) that there were no indications of an effect on urine resulting from exposure to the test compound.

Three of the five surviving high-dose males at 52 weeks had urines with specific gravities (1.009, 1.011 and 1.018) somewhat higher than normal, with the 1.018 value being the highest recorded in this study.

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		**Cardiovasc./Hemat.**		**Neurologic**
	Tongue	X	.Aorta*	XX	.Brain*†
	.Salivary glands*	XX	.Heart*	X	Periph. nerve*#
X	.Esophagus*	X	.Bone marrow*		Spinal cord (3 levels)*#
X	.Stomach*	X	.Lymph nodes*	X	.Pituitary*
X	.Duodenum*	XX	.Spleen*	X	Eyes (optic n.)*#
X	.Jejunum*	XX	.Thymus*		**Glandular**
X	.Ileum*		**Urogenital**	XX	.Adrenals*
	.Cecum*	XX	.Kidneys*†		Lacrimal gland#
X	.Colon*	X	.Urinary bladder*	X	Mammary gland*#
	.Rectum*	XX	.Testes*†		.Parathyroids*††
XX	Liver*†	X	Epididymides	XX	.Thyroids*††
X	Gall bladder*#	XX	Prostate		**Other**
XX	.Pancreas*		Seminal vesicle	X	Bone*#
	Respiratory	XX	Ovaries*†	X	Skeletal muscle*#
	.Trachea*	X	.Uterus*		Skin*#
XX	.Lung*				All gross lesions and masses*
	Nose°				
	Pharynx°				
	Larynx°				

* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies

Samples were embedded in paraplast, and 5 um sections were stained with haemalum (haemotoxylin?) eosin. Usually one section was made per organ, except for urinary bladders (3 or 4 sections). Extra kidney sections were stained by the Periodic Acid Schiff reaction. Fat tissue in the liver was stained with Oil Red O using 18 um frozen sections. The bones were decalcified using tetrasodium EDTA. Bone marrow smears were stained by the May-Gruenwald-Giemsa method.

Results:

Organ weights

Significant differences in mean absolute organ weights and/or organ-to-body-weight ratios between controls and high-dose dogs occurred with respect to the liver, thyroid, and thymus:

Organ weights and organ-to-body wt ratios (all survivors)

Test Group	Dietary Dose (ppm)	Mean Liver wt(g)	Liver to body wt ratio (g/kg)	Mean Thyroid wt(g)	Thyroid-body wt ratio (g/kg)	Mean Thymus wt(g)	Thymus-body wt ratio (g/kg)
1 Cont.	0	362.8	36.16	0.928	0.0930	8.69	0.872
2 Low	200	400.6	38.18	0.948	0.0912	9.52	0.901
3 Mid	600	382.3	41.13[a]	0.927	0.0996	8.22	0.874
4 High	1800†	415.5	52.50[c]	1.073	0.1323[c]	4.07[c]	0.479[c]

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.
[a]$p \leq 0.05$, [b]$p \leq 0.02$, [c]$p \leq 0.01$

If data from high-dose dog K679 (died during week 50) had been used in calculating the values above, the mean liver weight for high-dose dogs would have been 425.8 grams and the mean liver-to-body weight would have been 53.62 g/kg. High-dose dog K688 (weighing the least of any dog in this study at termination) had a 508 gram liver, and a liver-to-body weight ratio of 69.3 g/kg. However, even if data from K688 (and K679) are not included, the mean liver weight for high-dose dogs would be 406.2 grams, and the liver-to-body weight ratio would be 50.82 g/kg.

The following gives distribution of liver weights and relative liver-to-body weights in each group (calculated from data on p. 221 and 223 respectively):

Distribution of absolute liver weights/group

(ppm)	Below 300 g	301 - 350 g	351 - 400 g	401 - 450 g	451 - 500 g	Above 501 g
1 Cont. 0	1	5	3	3	0	0
2 Low 200	0	1	6	3	2	0
3 Mid 600	0	3	6	2	0	1
4 High 1800†	0	0	5	4	1	2*

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.
* Includes dog K679 (died wk 50) and dog K688.

Distribution of liver-to-body weight ratios (g/kg) per group

	(ppm)	Below 30	30.1-35	35.1-40	40.1-45	45.1-50	50.1-55	55.1-60	Above 60.1
1	Cont. 0	1	4	4	2	1	0	0	0
2	Low 200	0	4	3	3	2	0	0	0
3	Mid 600	0	1	4	5	1	1	0	0
4	High 1800†	0	0	0	3	0	5	1	3*

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.
* Includes dog K679 (died wk 50) and dog K688.

One dog (K682) in the 600 ppm (mid-dose) group had a liver-to body weight ratio of 54.1 g/kg, the highest value in this study outside the high-dose group. Without this value the mean for the group was 39.95 g/kg, still slightly above the means of 36.16 and 38.18 g/kg respectively for controls and low-dose dogs.

Thyroid

One male (K695) and one female in the high-dose group (K698) had high thyroid weights (2.04 and 1.66 g respectively). Without these dogs the mean thyroid weight for the remaining dogs was 0.892 grams, and the thyroid-to-body weight ratio 0.1143 g/kg. In the histopathology report K698 is reported (p. 232) as having a cyst in the thyroid.

Thymus

The following are the distributions for absolute and relative thymus weights in each group:

Distribution of absolute thymus weights/group

	(ppm)	0.0 - 2.49 g	2.5 - 4.99 g	5.0 - 7.49 g	7.5 - 9.99 g	10 g & above
1	Cont. 0	-	-	4	3	5
2	Low 200	-	-	3	3	6
3	Mid 600	-	2	4	2	4
4	High 1800†	4	3	5	-	-

† 1800 ppm wks 1-40; 3600 ppm wks 41-44; 5400 ppm wks 45-52.

Distribution of relative thymus weights(g/kg)/group

	(ppm)	0.0 - 0.249	0.25 - 0.499	0.50 - 0.749	0.75 - 0.999	1.00 & above
1	Cont. 0	-	1	3	4	4
2	Low 200	-	-	2	5	5
3	Mid 600	-	1	5	2	4
4	High 1800†	3	3	3	3	-

† 1800 ppm wks 1-40; 3600 ppm wks 41-44; 5400 ppm wks 45-52.

Males (but not females) of the 600 ppm (mid-dose) group had lower mean absolute and relative thymus weights than either

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their controls or males of the 200 ppm group, and this appeared to be part of a dose-related trend; from p. 225:

Mean absolute and relative thymus weights for males

	(ppm)	Absolute mean (g)	Relative mean (g/kg)
1 Cont.	0	8.65	0.832
2 Low	200	8.27	0.772
3 Mid	600	6.38	0.680
4 High	1800†	3.72	0.444

† 1800 ppm wks 1-40; 3600 ppm wks 41-44; 5400 ppm wks 45-52.

According to the text of the report (p. 48) there were no "notable differences" between absolute and relative organ weights for (among other organs) kidneys, adrenals and prostate. Spleens are not mentioned. Despite the lack of statistical significance, there may have been some effects on these organs and their absolute and/or relative weights:

Group organ weights and organ-to-body wt ratios

Test Group	Dietary Dose (ppm)	Kidneys mean wt (g)	Kidneys body wt ratio (g/kg)	Spleen mean wt (g)	Spleen body wt ratio (g/kg)	Adrenals mean wt (g)	Adrenals body wt ratio (g/kg)	Prostate mean wt (g)	Prostate body wt ratio (g/kg)
1 Cont.	0	54.7	5.47	30.3	3.04	1.282	0.1287	6.927	0.6668
2 Low	200	55.7	5.27	26.0	2.47	1.336	0.1278	6.903	0.6448
3 Mid	600	54.1	5.81	32.3	3.45	1.252	0.1343	6.015	0.6488
4 High	1800†	57.3	7.20	20.9	2.53	1.463	0.1785	4.346	0.5382

† 1800 ppm weeks 1-40; 3600 ppm weeks 41-44; 5400 ppm weeks 45-52.

Kidneys

The values given for the high-dose group above do not include data from dog K679 which died during week 50. With data from dog K679 (weight of kidneys 76 g; relative weight of 9.3 g/kg) the mean value would become 58.8 g, and the body wt ratio would be 7.38 g/kg.

The following are the absolute and relative kidney weight distributions/group (calculated from p. 221 & 223):

Distribution of absolute kidney weights/group

	(ppm)	45.0 - 49.9 g	50.0 - 54.9 g	55.0 - 59.9 g	60.0 - 64.9 g	65.0 - 69.9 g	70.0 - 74.9 g	75.0 & above
1 Cont.	0	1	6	3	2	-	-	-
2 Low	200	2	2	7	-	-	1	-
3 Mid	600	1	6	3	2	-	-	-
4 High	1800†	2	2	3	3	-	1	1

† 1800 ppm wks 1-40; 3600 ppm wks 41-44; 5400 ppm wks 45-52.

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Distribution of relative kidney weights (g/kg)/group

(ppm)	4.0 - 4.49	4.5 - 4.99	5.0 - 5.49	5.5 - 5.99	6.0 - 6.49	6.5 - 6.99	7.0 - 7.49	7.5 - 7.99	8.0 & above
1 Cont. 0	1	1	4	3	3	-	-	-	-
2 Low 200	-	4	4	3	1	-	-	-	-
3 Mid 600	-	-	1	8	2	-	-	-	-
4 High 1800†	-	-	-	-	3	3	-	1	5

† 1800 ppm wks 1-40; 3600 ppm wks 41-44; 5400 ppm wks 45-52.

Spleen

7/12 dogs in the high-dose group had terminal spleen weights of less than 20 grams. All the dogs in the other groups had terminal spleen weights of 20 grams or more. There appeared to be some (but not complete) correlation between terminal splenic and thymic weights in high-dose dogs, particularly as the 3 dogs (K671, K688 and K679) with lowest spleen weights also had the lowest thymus weights. From data on p. 221:

	Spleen weight(g)	Ranking	Thymus weight(g)	Ranking
K671	6	1	0.0	1.5
K688	8	2	0.0	1.5
K679	13	3	1.9	3
K672	17	4.5	6.7	11
K702	17	4.5	5.7	9.5
K711	18	6.5	3.5	5
K677	18	6.5	2.0	4
K665	22	8.5	5.7	9.5
K714	22	8.5	5.0	8
K698	26	10	4.3	6
K680	28	11	4.5	7
K695	48	12	7.4	12

Adrenals

Again, data from dog K679 (died week 50) is not included in the means from the high-dose group, but its inclusion makes little difference in this case (the mean goes from 1.463 to 1.476 grams).

The distribution of adrenal absolute weights/group is the following (calculated from data on p. 221):

Distribution of absolute adrenal weights/group

(ppm)	Below 0.99 g	0.99 - 1.24 g	1.25 - 1.49 g	1.50 - 1.74 g	1.75 - 1.99 g
1 Cont. 0	-	7	4	1	-
2 Low 200	1	2	7	1	-
3 Mid 600	-	5	7	-	-
4 High 1800†	1	2	2	4	2

† 1800 ppm wks 1-40; 3600 ppm wks 41-44; 5400 ppm wks 45-52.

Adrenals were only weighed from 11 dogs in both the low (200) and high-dose groups.

Prostate

Lower absolute and relative mean prostate weights in high-dose males were due mostly to data from dogs K671 and K711 (absolute prostate weights of 1.06 and 2.01 g respectively). Dog K671 weighed 6 kg (lowest of any male in the study), so nutritional factors may have been involved. However, K711 was the heaviest male (9.3 kg) in the high-dose group, so a similar explanation for its low prostate weight cannot be invoked. Mean absolute and relative prostate weights for the remaining 4 dogs were 5.96 g and 0.7325 g/kg respectively.

b. Gross pathology

From p. 46: nutritionally, most of the dogs in the control and low-dose groups were "normal" with two in the low-dose assessed as "normal to fat." Two dogs in the 600 ppm (mid-dose) group were thin, while most of the dogs in the high-dose group were thin, and one (K 688) was very thin and/or emaciated.

Atrophied thymus was noted on autopsy in two of the high-dose dogs (K671 and K688; on p. 223 for absolute organ weights the thymus weight for each of these dogs is listed as 0.0 grams). Other findings appeared to be sporadic and incidental.

c. Microscopic pathology

1) Non-neoplastic

Results are given only for the controls and high-dose dogs.

The only significant difference between these groups was a high incidence of atrophy of the thymus in high-dose dogs (the thymus was examined in 10 of the high-dose dogs; in all 10 it showed some degree of atrophy, as compared with an incidence of 1/12 in the controls).

2) Neoplastic

There is no indication that any neoplasms were found.

D. DISCUSSION:

This study has not demonstrated a NOEL, as at the lowest dietary dose level tested (200 ppm) there were significantly elevated mean cholesterol levels at 13, 26 and 52 weeks, and these were in each case part of a well-defined dose-related trend. No other effect was observed at 200 ppm.

At 600 ppm there were, in addition to elevated cholesterol levels, significantly elevated liver weights at termination,

and significantly higher mean N-demethylase activity. The reduced thymus weights in 2/6 males of the group have to be considered as significant, particularly in the absence of histopathology data from this group and the 100% incidence of atrophy of the thymus in high-dose dogs. Although not statistically significant, the fact that males (but not females) at 600 ppm showed a somewhat lower (25%) overall weight gain than did their controls is noteworthy. At week 1 (but not subsequently) 600 ppm dogs showed a statistically significant drop in RBC ChE activity (with respect to preexposure activity, but not with respect to control values) 1 hour after exposure (feeding?). RBC ChE activity had recovered to preexposure levels at 24 hours.

With respect to the high-dose animals, a major problem in interpreting the results of this study is in attempting to establish - where possible - what effects observed in the high-dose dogs were due to a long-term exposure (1-year) to Propoxur at 1800 ppm and above, and what were due to short-term (12-week) exposure to 3600+ ppm. Some of the effects (particularly the elevated adrenal and kidney weights in some high-dose dogs) may have been due to stress associated with symptoms of ChE inhibition.

Mean weight gains at week 40 week 40 (before the dietary concentration of Propoxur was raised from 1800 ppm) were depressed approximately 30% in high-dose males and by about 15% in females with respect to their controls. Although these depressions were not statistically significant, they were undoubtedly an effect of exposure to the test material, particularly as when the dietary level was raised to 3600 ppm, and then to 5400 ppm, the animals began losing weight.

Other effects in high-dose dogs were a 100% incidence of thymic atrophy. A non-significant reduction in mean spleen weights was probably related to this, as the three dogs with the greatest degree of thymic atrophy also had the lowest spleen weights.

Other findings at the high-dose level which were related to exposure to the test compound were an increase in mean thrombocyte counts and a reduction in mean serum protein, both of which were present throughout the study, and both of which became more pronounced after the dietary level of test material was raised. Elevations in GPT and AP activity were statistically significant only after the dietary level of Propoxur was raised to 3600 ppm.

The consistent depression in plasma ChE is somewhat surprising, as it has been usually assumed that this is a somewhat transient phenomenon with carbamates.

The short-term drop in RBC ChE activity at one week is interesting, particularly as it was not observed again. It may be that the dogs were metabolizing the propoxur more rapidly (also suggested by the increase in N-demethylase activity observed at termination), although a combination of factors (for example, the dogs, particularly in the high-dose group, could have modified their feeding habits to eat small amounts throughout the day, rather than consuming all their food when receiving it) may have been involved.

Because of the lack of a NOEL, as well as the lack of reporting of histopathology data (at least for the thymus) for low and mid-dose dogs, the study is classified as core supplementary data.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DEC 23 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Baygon 70% WP, Food Additive Petition

TO: Jay Ellenberger
Registration Division (TS-767)

FROM: Robert P. Zendzian PhD, Acting head 12/4/85
Review Section IV
Toxicology Branch
HED (TS-769)

THROUGH: Theodore M. Farber PhD, Chief
Toxicology Branch

Compound; Baygon (propoxur) Tox Chem #508

Registration #9H5199 Registrant; Mobay

Accession #073827 Tox Project #782

Action Requested

Company response to Agency's May 9, 1984 letter re:

1. Toxicity and doses in a mouse oncogenicity study consisting of stability data and rational as to why a bioavailability study is not necessary.

2. Statement re availability of chronic dog and chronic rat studies. These studies were required in and of themselves and to supply NOELs which had not been provided by subchronic dog and rat studies.

Conclusions

1. The stability data showed 94 to 99% nominal at day zero with a 14 to 36% loss of propoxur over the two week period following mixing. This does not account for the apparent ability of the mice to consume daily approximately 11 (male) and 13 (female) times the acute oral LD_{50} during the course of the oncogenicity study.

The rational proposed for the apparent decease in lethality is not applicable to this case since it concerns compounds where cumulative lethality can be produced by single doses over a period of days or weeks. This is not possible with short acting carbamates nor is it the concern with propoxur. The question here concerns lethality during each single day of the study.

It is well established that rodents can consume more than an acute LD_{50} of a rapidly metabolized carbamate cholinesterase inhibitor in a single day. In the Baygon rat study at the high dose of 50ppm the rats consumed approximately 2.5 times the LD_{50}. However, the magnitude of the increase over the acute LD_{50} in this mouse study is much greator than any previously reported and requires independent experimental proof.

2. The chronic dog study (one-year) was found in Accession Number 256151 as noted by the Registrant. However, this entire package was never submitted to Toxicology Branch for review. This data package must be submitted formally to HED by Registration Division so that it may be reviewed.

The chronic rat study showed an oncogenic response which will be evaluated by the Toxicology Branch ad hoc commitee. If this response is considered indicative of oncogenicity by the compound it will have a significant effect on a food additive petition.

Recommendation

1. In order to validate the mouse oncogenicity study, the Registrant must suggest and perform a short term feeding study in mice that demonstrates their ability to consume, without signs of toxicity including lethality, the high doses used in the chronic feeding study.

2. Registration Division must formally submit to HED the data package submitted by the Registrant and filed under accession number 256151 so that it may be reviewed. This package is dated December 1984.

3. No further registration actions should be granted on Baygon (propoxur) until Toxicology Branch has completed its determination as to the oncogenicity of the compound. This is particularly important in relation to the subject food additive petition.

Background and Discussion

1. In relation to the mouse feeding study, in 1982 Mobay submitted the following study;

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BOE 5812315 (Propoxur, the Active Ingredient of Baygon) Chronic Toxicity Study in Mice (Two Year Feeding Experiment). E. Bomhard and E. Loeser, Histopathology D.R. Patterson Bayer Report No. 9954, Bayer AG, Institut Fuer Toxikologic, Wappertal, F.R.G., May 12, 1982

In my review of the study I noted that the high dose animals consumed calculated propoxur doses of 1191 mg/kg/day for the males and 1374 mg/kg/ day for the females (Zendzian (1982). This was 11 to 13 times the acute oral LD_{50} for rats. Subsiquently the Registrant provided information that showed that the mouse was at least equally if not more sensitive acutely to propoxur. An explanation of this discrepency was requested. Included was a request for additional information on stability tests of propoxur in the feed.

The Registrant submitted copies of the hand written notes of a single chemical analysis of propoxur stability in feed made during the mouse chronic study. These notes showed that the concentration of the three doses was 94 to 99 % of nominal at day zero and decreased to 64 to 86% at 14 days. If correct, this does not provide an explaination of the lack of lethality in this study.

The Registrant submitted data comparing the acute oral LD_{50}s of several compounds with their 90-day oral LD_{50}s (90 consecutive daily oral doses). With many compounds it is possible to give many times the acute oral LD_{50} over a period of 90 days by giving a fraction of that dose daily until the cumulative toxicity of the compound produces death. This is well established but has nothing to do with the present case. Cumulative lethality cannot be demonstrated in this fashion with rapidly metabolized carbamates such as propoxur which have their toxic effects completely reversed in less than 24 hours. However, there is always a practical limit to the amount which can be given in the feed in a single day without producing lethality. In general rodents eat most of their food in two periods, at the beginning and the end of their period of darkness. Some additional eating takes place throughout the day but the amount of carbamate that can be taken in daily in the feed without showing toxicity is limited to the amount taken during a single heavy feeding period. In the propoxur study in the rat, the high dose of 50ppm is approximately 2.5 times the rat oral LD_{50}. However the excess compound intake in the mouse study is far beyond any previously reported.

Considering the circumstances, the Agency requires independent experimental proof that the mice on 6000 ppm propoxur in the diet can consume the dose calculated from the food consumption in this study and have no demonstrated toxic signs much less have an extended life span as shown in the mouse study.

The Registrant must develop and perform a short term mouse feeding study that shows conclusively that mice can tolerate 6000 ppm propoxur in the diet. It is suggested that the study not be performed in the laboratory (Bayer AG, Institut Fuer Toxikologic, Wappertal, F.R.G.) which performed the questionable mouse feeding study.

2. In support of earlier registration requests Mobay had submitted subchronic studies in the dog and rat which failed to demonstrate a NOEL for cholinesterse inhibition, the most sensitive toxic effect. It was concluded by the Agency reviewers that chronic studies in these two species could supply these deficiencies. In this submission Mobay noted that the following studies had been submitted to the Agency in 1984.

"(4) The rat and dog chronic feeding studies have been submitted and are on file with the Agency under:

Report No. 86665, "Propoxur Chronic Toxicity Study on Dogs". EPA Accession No. 256151.

Report No. 88501, 'Propoxur Chronic Toxicological Study with Rats". Submitted to the Agency October 15, 1984 in the Compilation of data entitled, "Toxicology Studies on Propoxur and its Metabolites", dated October 12, 1984."

No record of receipt or review of the chronic dog study could be found in the Toxicology Branch files and a copy of Accession No. 256151 was obtained from Registration Division. The submission was found to consist of 13 acute toxicity studies, an applicator exposure study, a 5-day oral rat study, the subject one-year dog study, five mutagenicity studies and an enzyme induction study. Toxicology Branch has no record of receipt or review of any of these studies.

Registration Division must formally submit to HED this data package, filed under Accession Number 256151, so that it may be reviewed. This package is dated December 1984.

The referenced chronic rat study has been reviewed by Toxicology Branch (Backus 1985). Backus concluded that;

"The 2-year rat feeding study is Core Minimum Data as an oncogenicity study. Both male and female rats showed a dose-related increase in incidence of papillomas and carcinomas of the bladder. All carcinomas and all but one papillonma occured in the high dose (5000 ppm) rats, with only one male rat at the 1000 ppm found to have a bladder papillonoma. There was also an dose-related increase incidences of urothelial hyperplasia of the bladder in both 1000 and 5000 ppm rats of both sexes, with almost all rats in the 5000 ppm group showing this finding at autopsy. Females in the 5000 ppm group showed increased incidence of uterine carcinoma, which may also be an oncogenic effect."

The results of this study will be evaluated by the Toxicology Branch ad hoc commitee. If this response is considered indicative of oncogenicity by the compound it will have a significant effect on a food additive petition.

Citations

Memo Zendzian to Ellenberger, Aug 16, 1982
Baygon® PP# 2F1244, Review of Two-year Mouse Oncogenicity Study and Teratology Study

Memo Backus to Ellenberger, Jan 16, 1985
Baygon Oncogenicity, Mutagenicity and Metabolite Studies
Caswell #508, 508A, 507A, 109A 495D

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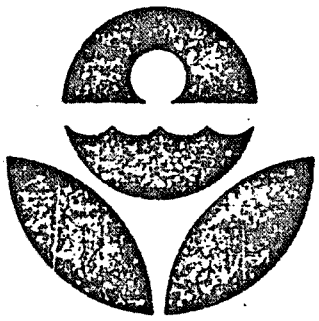

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HUMAN SAFETY DATA

December, 1984

MOBAY CHEMICAL CORPORATION
AGRICULTURAL CHEMICALS DIVISION
Kansas City, MO 64120

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December, 1984

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Reviewed by: Byron T. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) 12.17.86

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DATA EVALUATION REPORT XXI

STUDY TYPE: Mutagenicity (2) - Rec assay & Ames study

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: Propoxur

SYNONYMS: 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): Report no. 103

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: NITOKUNG Agricultural Chemicals Institute
Laboratory of Toxicology

TITLE OF REPORT: Propoxur - Mutagenicity test on bacterial systems

AUTHOR(S): Inukai, H., and Iyatomi, A.

REPORT ISSUED: February 24, 1978

CLASSIFICATION: Not acceptable (both studies)

CONCLUSIONS AND RECOMMENDATIONS:

1. While there were no indications of mutagenic activity for the test compound in either of these two studies (a rec assay on *B. subtilis* comparing a repair deficient strain, NIG45, with a wild-type strain, NIG17, which can repair damage to DNA; and an Ames reversion assay utilizing *S. typhimurium* strains TA1535, TA1537, TA98 and TA100 both with and without rat and mouse S9) there is no indication in either of the two studies that the test material was applied at a cytotoxic level, or that the studies were run with any sort of adequate replication. It is also noted that the rec assay was not done with metabolic activation (there was no simultaneous exposure to rat and/or mouse S9).

2. These two studies were previously reviewed (W. Dykstra, Oct. 17, 1979) and were classified as Core Minimum (Acceptable) Data, however, neither of these studies is acceptable according to current criteria. Both of these studies are reclassified to "Not Acceptable."

A. MATERIALS:

1. Test compound: technical grade propoxur, 98.0% pure. No physical description given.

2. Positive controls: Mitomycin C (MC) used in the Rec assay; acetylaminofluorene (AAF), used with rat S9 mix and S. typhimurium strains TA98 and TA100; dimethylnitrosamine (DMNA) used with mouse S9 and strains TA1535 and TA100; Furylfuramide (AF-2) used without activation for strains TA98 and TA100; 9-aminoacridine-HCl (9-AA) used without activation for strain TA1537; N-methyl-N'-nitro-N-nitroso-guanidine (NTG) used without activation for strain TA1535.

B. STUDY DESIGN:

1. Rec Assay: This assay was performed on two strains of B. subtilis, NIG45, a repair deficient strain (rec-) which is unable to completely repair damaged DNA, and NIG17, a wild-type strain (rec+) which has normal DNA repair capability. Overnight cultures of both strains were streaked on the surface of solid agar broth. Paper disks which had been "immersed with" (to which had been added?) 3, 30, or 300 ug of propoxur, or 0.3 ug MC (positive control), were put on the edges of streaks. Plates were incubated (37° C) overnight and the "lengths" (diameters?) of the zone of inhibition were measured.

2. Reversion Assay with in vitro metabolic activation: S-9 was prepared from liver homogenates of rats or mice (no strains are reported) which had been treated with phenobarbital. "For mutagenicity test with the S-9 fraction, 0.1 ml of each tester strain, 0.3 ml of S-9 mixture and 0.1 ml of the tested compound were spreaded (sic) by a glass spreader. The plates were incubated at 37° C for 48 hours and then revertant colonies on the plate were counted." There is no indication as to what growth phase the strains were in. Doses of propoxur tested were 0.1, 10 and 1000 ug/plate (with metabolic activation) and 1000 ug/plate (without metabolic activation).

C. RESULTS:

1. Rec Assay: There was no "length" (diameter?) of inhibition in either of the two B. subtilis strains associated with any of the dose levels (3, 30 or 300 ug/disk) of propoxur. The "length" of inhibition for the disk containing 0.3 ug MC was 1 mm for NIG17 (rec+) and 11 mm for NIG45.

2. Reversion Assay: with rat S-9; from table 4:

test material	ug/ plate	S-9 Mix	Revertant colonies per plate TA1535	TA1537	TA98	TA100
propoxur	1000	+	8	8	44	263
"	10	+	6	7	30	249
"	0.1	+	9	7	29	281
"	1000	-	8	7	20	193
-	-	+	5	7	25	291
AAF	50	+	-	-	>1000	>1000
AF-2	0.1	-	-	-	195	>1000
9-AA	200	-	-	>1000	-	-
NTG	10	-	>1000	-	-	-

With mouse S9 (from table 5):

test material	ug/ plate	S-9 Mix	Revertant colonies per plate TA1535	TA1537	TA98	TA100
propoxur	1000	+	2	6	10	160
"	10	+	6	4	29	192
"	0.1	+	3	23	13	224
"	1000	-	5	12	18	299
-	-	+	12	4	23	260
DMNA	50	+	>1000	-	-	>1000
AF-2	0.1	-	-	-	121	>1000
9-AA	200	-	-	>1000	-	-
NTG	10	-	>1000	-	-	-

D. DISCUSSION:

While there were no indications of mutagenic activity for the test compound in either of these two studies (a rec assay on B. subtilis comparing a repair deficient strain, NIG45, with a wild-type strain, NIG17, which can repair damage to DNA; and an Ames reversion assay utilizing S. typhimurium strains TA1535, TA1537, TA98 and TA100 both with and without rat and mouse S9) there is no indication in either of the two studies (either from concurrent or preliminary studies) that the propoxur was applied at a cytotoxic level, or that the studies were run in duplicate (or even whether there was more than one plate/dosage level) or with any sort of adequate replication. It is also noted that the rec assay was not done with metabolic activation (there was no simultaneous exposure to rat and/or mouse S9).

These two studies were previously reviewed (W. Dykstra, Oct. 17, 1979) and were classified as Core Minimum (Acceptable) Data, however, neither of these studies is acceptable according to current criteria. Both of these studies are reclassified to "Not Acceptable."

Reviewed by: Byron T. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) 12.17.86

005692

DATA EVALUATION REPORT XXII

STUDY TYPE: Mutagenicity - micronucleus (in vivo) - mouse

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: BOE 5812315

SYNONYMS: propoxur, baygon, 2-isopropoxyphenyl-N-methyl carbamate

STUDY NUMBER(S): EHR file no. 2347

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Micronucleus test on mouse to evaluate BOE 5812315 for mutagenic potential

AUTHOR(S): Herbold, B.

REPORT ISSUED: 6/27/80

CLASSIFICATION: Acceptable

CONCLUSIONS:

1. No mutagenic effect for BOE 5812315 was observed in this assay at doses of up to and including 2 x 10 mg/kg.

A. MATERIALS:

1. Test compound: BOE 5812315, common name propoxur, identified as the insecticidally active ingredient of Baygon and Unden, with a purity of 99.2%. No physical description given.

2. Positive control: ®Trenimon, Batch 04061962, identified as a "former cytostatic drug and proven mutagen which has a direct alkylating effect."

3. Test animals: Male and female mice of the NMRI strain, from S. Ivanovas GmbH, Kisslegg/Allgäu. At the start of the study they were 8-12 weeks old, and weighed 20-36 grams.

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B. STUDY DESIGN:

1. Animal assignment: mice were randomly assigned to the test groups, each consisting of 5 males and 5 females.

2. Test material preparation and administration: the test material was suspended in a 0.5% Cremophor emulsion and was orally administered by gavage. Negative controls received the emulsion only, while the positive control group was dosed with Trenimon in demineralized water. Dosage volumes were constant at 10 ml/kg body weight. The maximum dosage of propoxur given (10 mg/kg) was on the basis of a preliminary study in which there had been "mild symptoms" at this dose level. The mice were sacrificed 6 hrs after receiving the second dose.

3. Statistics: "The results were statistically analyzed by the non-parametric ranking test of NEMENIY. A difference was considered to be statistically significant when the probability was less than 5% ($p < 0.05$). The positive control was excluded from this consideration."

4. Quality assurance: no quality assurance statement is provided.

C. METHODS AND RESULTS:

1. Dosages: A negative control group received the carrier (Cremophor emulsion) only, two groups received either two 5 mg/kg or two 10 mg/kg dosages of the test material 24 hrs apart, while the fourth group received two 0.125 mg/kg dosages of the positive control (Trenimon) 24 hours apart.

   Toxicity: Although 2 x 10 mg/kg propoxur had induced mild symptoms in a preliminary test, no signs of toxicity were observed at this level (or at 2 x 5 mg/kg) in the study. Behavior, appetite and physical appearance are stated as remaining normal. There was no mortality.

2. Sacrifice and evaluations: Mice were sacrificed by decapitation 6 hours after receiving a second dose. Bone marrow (from the femur) was processed and slides were prepared. 1000 polychromatic erythrocytes/mouse were counted and the incidence of cells with micronuclei was determined. Also, the number of normochromatic erythrocytes per 1000 polychromatic erythrocytes/mouse was determined, and the ratio was calculated.

Results:

The following is a summary of table 5, with additional material (group ranges) from tables 1-4:

Group and Dosage	group total number of scored polychromatic RBC's	Normochromatic erythrocytes/ 1000 polychromatic RBC's & group range	Number of cells with micronuclei	
			per 1000 normochromatic RBC's & group range	per 1000 polychromatic RBC's & group range
I. Negative Control	10,000	810.6 505 - 1194	1.31 0 - 5.21	1.6 0 - 3
II. BOE 5812315 2 x 5 mg/kg	10,000	814.1 300 - 1132	1.28 0 - 3.41	0.6 0 - 3
III. BOE 5812315 2 x 10 mg/kg	10,000	1033.2 551 - 1486	0.93 0 - 3.71	1.4 0 - 3
IV. Trenimon 2 x 0.125 mg/kg	10,000	1065.8 382 - 1887	1.42 0 - 3.47	5.8 0 - 12

Two sample T tests comparing the group means of number of cells per 1000 polychromatic erythrocytes with that for negative controls gave the following p values:

Group and Dosage	p value for equality of group means of no. cells/1000 polychromatic RBC's with that of negative controls
II. BOE 5812315 2 x 5 mg/kg	0.0624
III. BOE 5812315 2 x 10 mg/kg	0.6823
IV. Trenimon 2 x 0.125 mg/kg	0.0048*

*Unequal variances, test for equality of variance p = 0.0014.

Only the mean of the Trenimon group was significantly different ($p \leq 0.5$) from that of the negative controls.

D. DISCUSSION:

The study is acceptable. No mutagenic effect was observed in this assay as a result of exposure to either two 5 mg/kg or two 10 mg/kg oral dosages (with a 24 hr interval between) of the test material. The positive control elicited an appropriate response.

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Section 3, Tox. Branch (TS-769C) 12.17.86

005692

DATA EVALUATION REPORT XXIII

STUDY TYPE: Mutagenicity - Ames study

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: Carbamate UN technical

SYNONYMS: BOQ 5812315, 2-isopropoxy-phenyl-N-methylcarbamate, propoxur, baygon

STUDY NUMBER(S): Report no. 11301

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Salmonella/Microscome test to evaluate for point mutation

AUTHOR(S): Herbold, B.

REPORT ISSUED: 12/6/82

CLASSIFICATION: Acceptable

CONCLUSIONS:

1. No mutagenic effect for the test material was observed with and without metabolic activation (S9 prepared from livers of male Sprague-Dawley rats) in replicate studies at doses of up to 12,500 mcg/plate. There was a sufficient level of cytotoxicity in all strains of S. typhimurium used (TA 1535, TA 100, TA 1537, TA98).

A. MATERIALS:

1. Test compound: Carbamate UN technical, a mixture of 5 batches, nos. 100201, 100216, 100222, 100226 and 100234, with a purity of 98.6%. No physical description given.

2. Positive controls: Endoxan, batch 0378, with active ingredient cyclophosphamide; Trypaflavine, batch 0282995, a frameshift promutagen; 2-aminoanthracene (2-AA), batch 10630.

3. Test organisms: Histidine-deficient Salmonella typhimurium strains TA 1535, TA 1537, TA100 and TA 98. The bacterial suspensions used were obtained from 17-hour cultures.

4. S-9 Mix: Prepared from the livers of at least six adult male 200-300 g. Sprague-Dawley rats. Each had received a single IP injection of aroclor 1254 at 500 mg/kg body weight five days before being sacrificed.

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B. STUDY DESIGN:

1. Test material preparation: DMSO was used as the solvent for the test material. DMSO was also the solvent for the positive controls trypaflavine and 2-aminoanthracene. Demineralized water was used for the positive control Endoxan.

2. Statistics: There is no indication, either in the text or in the results, that the data were statistically analyzed.

3. Quality assurance: no quality assurance statement is provided.

C. METHODS AND RESULTS:

1. Dosages: The methodology was that of Ames. There were two exposure series. In the first, dosages of the test material were 0, 20, 100, 500, 2500 and 12500 micrograms/plate. In the second series, dosages were 0, 750, 1500, 3000, 6000 and 12000 micrograms/plate. All dosages were run both with and without S-9 mix. There were appropriate positive controls.

2. Results: Refer to the appended copies of tables 1-8.

D. DISCUSSION:

There was no evidence, either with or without concurrent exposure to S-9 mix, of any mutagenic effect resulting from the test material. Cytotoxicity was evident for at least the highest (12000 or 12500 micrograms/plate) dosage level of the test material in each assay. The positive controls elicited an appropriate level of response.

The study is acceptable.

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Pages 96 through 103 are not included in this copy.

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___ Description of the product manufacturing process

___ Description of product quality control procedures

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___ The product confidential statement of formula

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Reviewed by: Byron Backus
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005692

DATA EVALUATION REPORT XXIV

STUDY TYPE: Mutagenicity - DNA (POL) repair in E. coli TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151 MRID NO.: not given

TEST MATERIAL: Carbamate UN technical

SYNONYMS: BOQ 5812315, 2-isopropoxy-phenyl-N-methylcarbamate, propoxur, baygon

STUDY NUMBER(S): Report no. 11403

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Pol/A_1- test on E. coli for potential DNA damage

AUTHOR(S): Herbold, B.

REPORT ISSUED: 1/6/83

CLASSIFICATION: Not acceptable

CONCLUSIONS:

1. While no mutagenic effect from the test material was observed in this assay, there was no evidence of any inhibition around the filter paper containing the test material at the highest dose levels used (1 mg/plate in the first assay, 10 mg/plate in the second assay), with or without S-9 activation.

A. MATERIALS:

1. Test compound: Carbamate UN technical, a mixed batch with a content of 98.5/98.6%. No physical description given.

2. Positive control: Methyl methane sulphonate (MMS), batch 1171879, a known alkylating agent and mutagen.

3. Negative control: Chloramphenicol, with a bacteriotoxic effect on gram positive bacteria.

4. Test organisms: Two strains of E. coli, one (K 12)p 3478 (polA_1-) of which is repair deficient, the other, W3110 (polA+) is "repair-proficient."

5. S-9 Mix: Prepared from the livers of at least six adult male 200-300 g. Sprague-Dawley rats. Each had received a single IP injection of aroclor 1254 at 500 mg/kg body weight five days before being sacrificed.

005692

B. STUDY DESIGN:

1. Test material preparation: DMSO was used as the solvent for the test material and chloramphenicol.

2. Statistics: There is no indication, either in the text or in the results, that the data were statistically analyzed.

3. Quality assurance: no quality assurance statement is provided.

C. METHODS AND RESULTS:

1. Methods: The substance was placed on a small round filter paper which was laid on a nutrient broth agar plate already inoculated with one of the two E. coli strains and containing, when appropriate, the S-9 mix. After plates had been incubated for 24 hrs at 37° C the zone of inhibition (if any) around the filter paper was measured and the result from the $polA_1$- was compared with that from corresponding polA+. An increase in inhibition around the $polA_1$- strain relative to that for the polA+ would be evidence of mutagenic activity.

2. Dosages: In the first assay the following doses of test material were used: 62.5, 125, 250, 500 and 1000 ug/plate with and without S-9 mix. There was a solvent control, a negative control (chloramphenicol at 30 ug/plate) and a positive control (MMS at 10 ul/plate). In the second assay the test material doses were 625, 1250, 2500, 5000 and 10000 ug/plate, with and without S-9 mix. Again there was a solvent control, and the same negative and positive controls (and dose levels) as in the first assay.

3. Results: Representative results from the first assay (without S-9) are shown below (from table 1):

dose in ug/plate	strain	inhibition zone diameter in mm	difference between strains
solvent control	$polA_1$-	0	0
	polA+	0	
1000 Carbamate UN (highest dose)	$polA_1$-	0	0
	polA+	0	
30 chloramphenicol	$polA_1$-	15.2	-13.3
	polA+	28.5	
10 ul MMS	$polA_1$-	57.7	+17.6
	polA+	40.1	

Representative results from the first assay (with S-9) are shown below (from table 2):

dose in ug/plate	strain	inhibition zone diameter in mm	difference between strains
solvent control	$polA_1$-	0	0
	polA+	0	
1000 Carbamate UN (highest dose)	$polA_1$-	0	0
	polA+	0	
30 chloramphenicol	$polA_1$-	17.3	-10.3
	polA+	27.6	
10 ul MMS	$polA_1$-	59.9	+20.1
	polA+	39.8	

From the second assay without S-9 mix (from table 3):

dose in ug/plate	strain	inhibition zone diameter in mm	difference between strains
solvent control	$polA_1$-	0	0
	polA+	0	
10000 Carbamate UN (highest dose)	$polA_1$-	0	0
	polA+	0	
30 chloramphenicol	$polA_1$-	18.1	-12.3
	polA+	30.4	
10 ul MMS	$polA_1$-	52.3	+13.1
	polA+	39.2	

Representative results from the second assay (with S-9) are shown below (from table 4):

dose in ug/plate	strain	inhibition zone diameter in mm	difference between strains
solvent control	$polA_1$-	0	0
	polA+	0	
10000 Carbamate UN (highest dose)	$polA_1$-	0	0
	polA+	0	
30 chloramphenicol	$polA_1$-	19.5	-7.0
	polA+	26.5	
10 ul MMS	$polA_1$-	60.0	+20.5
	polA+	39.5	

D. DISCUSSION:

While there was no evidence, either with or without concurrent exposure to S-9, of a mutagenic effect from the test substance, there were no indications of cytotoxicity at the highest dose levels tested (1000 ug/plate in the first assay, and 10,000 ug/plate in the second assay) in either of the two strains.

The study is therefore considered as inconclusive, and not acceptable.

Reviewed by: Byron T. Backus
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Section 3, Tox. Branch (TS-769C) M van Gemert 12.17.86

005692

DATA EVALUATION REPORT XXV

STUDY TYPE: Mutagenicity - Ames study & Rec Assay

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: Propoxur

SYNONYMS: o-isopropoxyphenyl methylcarbamate

STUDY NUMBER(S): Report no. 84124

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Institute of Toxicology (Japan)

TITLE OF REPORT: Propoxur Microbial Mutagenicity Study

AUTHOR(S): Ohta, T. and Moriya, M.

REPORT ISSUED: 2/28/83

CLASSIFICATION: Rec Assay: Not Acceptable
Ames Assay: Acceptable

CONCLUSIONS:

1. In the Rec assay with B. subtilis strains M45 and H17 no mutagenic effect for the test material was observed without S9 activation at doses of up to 10,000 ug/disk. However, there was no evidence of any cytotoxicity at the highest dose level, and the assay was not run in replicate.

2. In the Ames assay no mutagenic effect for the test material was observed with or without metabolic activation (S9 prepared from livers of male Sprague-Dawley rats) in replicate at doses of up 25,000 ug/plate. There was sufficient cytotoxicity at the high dose levels in all strains of S. typhimurium (TA 100, TA 1535, TA 1538, TA 98, TA 1537) as well as the tryptophan-requiring E. coli (WP2 hcr) used. Positive controls elicited the appropriate responses.

A. MATERIALS:

1. Test compound: Propoxur, identified as 98% pure. No physical description is given. The test compound was dissolved in DMSO in this study.

2. Positive controls: Kanamycin and Mitomycin C were used as negative and positive control respectively in the rec assay. 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide, AF-2; N-ethyl-N'-nitro-N-nitrosoguanidine, ENNG; 2-nitrofluorene, 2-NF;

CC-192

and 2-aminoanthracene, 2-AA were used as positive controls in the Ames assay.

3. Test organisms: For the rec assay Bacillus subtilis strains H17 (rec$^+$) and M45 (rec$^-$) were used. For the Ames assay histidine-deficient Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 were used, as well as E. coli WP2 hcr requiring tryptophan.

4. S-9 Mix (for the Ames assay) was prepared from the livers of an unspecified number of 7-week old Sprague-Dawley male rats, average weight 236 g. Each had received a single IP injection of aroclor 1254 at 500 mg/kg body weight five days before sacrifice.

B. STUDY DESIGN:

1. Test material preparation: The propoxur was dissolved in DMSO in both assays. It is noted that propoxur was soluble in DMSO at up to 500 mg/ml, and this established the limit of 10 mg/disk (0.02 ml) in the rec assay. However, in the Ames assay 50,000 ug/plate resulted in "crystalization" of the compound, so 25,000 ug/plate was the maximum dose used.

2. Statistics: There is no indication, either in the text or in the results, that the data were statistically analyzed in either of the two assays.

3. Quality assurance: no quality assurance statement is provided.

C. METHODS AND RESULTS:

1. Rec assay: "Frozen cultures of the two strains...were thawed and streaked with the use of small pipettes onto the surface of a B-2 agar plate with care not to let them touch each other. A filter paper disk, 10 mm in diameter, was soaked with 0.02 ml of the compound and was placed so as to cover the starting parts of the streaks. The length of the inhibitory zone of each streak was measured after overnight incubation at 37° C."

   Results: There was no inhibitory zone around the disk at any concentration of propoxur. With the Kanamycin (10 ug/disk) there was an inhibitory zone of 5.5 mm for the M45 and 5 mm for the H17. With Mitomycin C (0.1 ug/disk) the zones of inhibition were 7 and 1 mm for the M45 and H17 respectively.

2. Ames assay: The six strains stored at -80° C were inoculated on nutrient broth liquid and cultured overnight at 37° C. Soft agar ("top agar") was mixed with appropriate amounts of bacterial suspension, a solution of the compound and 100 mM sodium phosphate pH 7.4 or the S9 mix, and was then poured on a minimal agar plate. Plates were incubated at 37° C for 2

days and revertants were counted.

2. Results: Refer to the appended copy of table 2.

D. DISCUSSION:

No mutagenic effect for propoxur was observed in the Rec assay with B. subtilis strains M45 and H17 at doses of up to 10,000 ug/disk without S9 activation. However, there was no evidence of cytotoxicity at the highest dose level, and the assay was not run in replicate.

No mutagenic effect for the test material was observed in the Ames assay with or without metabolic activation (S9 prepared from livers of male Sprague-Dawley rats) in replicate doses of up to 25,000 ug/plate. There was sufficient cytotoxicity at the high dose levels in all strains of S. typhimurium (TA 100, TA 1535, TA 1538, TA 98, TA 1537) as well as for the tryptophan-requiring E. coli (WP2 hcr). Positive controls elicited the appropriate mutagenic responses.

Propoxur Toxicology Reviews

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Reviewed by: Byron Backus
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Secondary reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) MvanGemert 12.17.86

005692

DATA EVALUATION REPORT XXVI

STUDY TYPE: 5-day oral dosing & liver microsomal enzyme induction - rat

TOX. CHEM. NO.: 508

ACCESSION NUMBER: 256151

MRID NO.: not given

TEST MATERIAL: BOQ 5812315

SYNONYMS: Propoxur, Baygon,

STUDY NUMBER(S): 10976

SPONSOR: Mobay Chemical Corporation

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: BOQ 5812315 (Propoxur, the active ingredient of Baygon) tests for induction of liver microsomal enzymes

AUTHOR(S): Mihail, F.

REPORT ISSUED: 06/29/82

CLASSIFICATION: Core Supplementary Data

CONCLUSIONS:

1. There was no evidence following 5-day dosage of the test material at 15 or 30 mg/kg/day of induction of any of the following liver enzymes: aminopyrine-N-demethylase, p-nitroanisole-O-demethylase or cytochrome P-450.

2. There was no indication that 5-day oral exposure to the test material had any effect on either absolute liver weight or the liver-to-body weight ratio.

3. Since body weights are reported only to the nearest multiple of of 5 grams, and because the rats could have received a higher daily dosage of the test material if it had been mixed with their diet, the study is classified as supplementary.

005692

A. MATERIALS:

1. Test compound: BOQ 5812315 (propoxur, identified as the active ingredient of Baygon), composite sample of batches 234001222/226, with a purity of 99.4%.

2. Positive control: Phenobarbital sodium (sodium salt of 5-ethyl-5-phenylbarbituric acid) from Merck. Purity not specified.

3. Test animals: Species: rat, Strain: BOR:WISW(SPF-CPB), source: Winkelmann in Borchen, West Germany. "At the start of the experiment, the animals weighed an average of 150-180 g."

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Material received	Daily dose (mg/kg)	No. of rats male	female
I	vehicle only	-	10	10
II	BOQ 5812315	15	10	10
III	BOQ 5812315	30	10	10
IV	Phenobarbital sodium	50	10	10

2. Dose preparation: "test compounds were administered to the animals per os with an oral intubation tube once per day for a period of 5 days." "The test compound samples were formulated with Cremophor EL (5 drops per 10 ml formulation) in distilled water in such a way that all doses were administered in a constant volume of 10 ml/kg body weight."

3. Animals received food ("Altromin 1324 feed for rats and mice") and water ad libitum.

4. Statistics: the arithmetic group means, standard deviations, and upper and lower confidence limits at the confidence level of 1 - alpha = 95% and 1 - alpha = 99% were calculated.

"The data for the control population was compared with the corresponding data for the test populations by applying the significance test (U test) of Mann, Whitney, and Wilcoxon at the significance level of alpha = 5% and alpha = 1%.

5. Quality assurance: There is no quality assurance statement.

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C. METHODS AND RESULTS:

1. Observations: animals were apparently observed daily.

   Administration of the BOQ 5812315 at 15 and 30 mg/kg is reported (p. 8) as causing tremors which lasted for an average of 1.5 hrs. Administration of the positive control (phenobarbital sodium) is reported as having induced sedation which persisted up to the next treatment.

   There was no mortality.

2. Body weight: Individual animals were weighed at the beginning and at the end of the "week" (presumably a 5-day period) of treatment.

   Results: while there were no significant differences between dose group means and those of controls, body weights and mean weight gains for females at 15 and 30 mg/kg/day of BOQ 5812315 tended to be somewhat lower than those of both negative and positive controls.

   Mean body weight gains (grams)

Group	Males	Females
I Negative controls	12	6
II BOQ 5812315 15 mg/kg/day	14	1
III BOQ 5812315 30 mg/kg/day	11	1
IV Phenobarbital sodium	15	9

   In the individual data (p. 19-20 and p. 25-26) body weights are given in multiples of 5 grams, and this reviewer believes this may have been a source of additional variation.

3. Food consumption: there are no food consumption data.

4. No blood was collected.

5. Sacrifice: "Three hours after the final administration, the animals were narcotized with ether and exsanguinated by cardiopuncture. The livers of all rats were removed and weighed."

   Results: The liver weights of male rats which had received 50 mg/kg/day sodium phenobarbital were significantly ($p < 0.01$) elevated. Liver weights for female rats receiving sodium phenobarbital were elevated, but not significantly. Mean liver weights for rats which received the test material were somewhat lower than those of controls, but the differences were not statistically significant.

6. Laboratory tests: Three portions of each liver were prepared and the following liver microsomal enzyme activities were assayed: 1) aminopyrine-N-demethylase; 2) p-nitroanisole-O-demethylase and 3) cytochrome P-450.

Results:

The two groups receiving the test material showed no significant differences for any of the mean enzyme activities with respect to the negative control group. Rats dosed with sodium phenobarbital showed noticeable (and presumably statistically significant) increases for all 3 enzyme activities. The following are from p. 27:

Males	Amino-pyrine-N-demethy-lase Nmol/g/min	p-nitro-anisole-O-demethy-lase Nmol/g/min	P450 Nmol/g/min
Group	(Standard deviations in parenthesis)		
I Negative controls	124.3(24.5)	8.0(1.2)	25.8(2.5)
II BOQ 5812315 15 mg	107.4(21.2)	8.6(1.4)	26.7(3.5)
III BOQ 5812315 30 mg	122.5(35.7)	8.3(1.6)	26.5(2.8)
IV Phenobarbital sodium	273.7(45.1)	36.1(5.5)	55.1(8.1)

Females	Amino-pyrine-N-demethy-lase Nmol/g/min	p-nitro-anisole-O-demethy-lase Nmol/g/min	P450 Nmol/g/min
Group			
I Negative controls	64.6(14.1)	8.1(1.4)	25.7(3.7)
II BOQ 5812315 15 mg	65.0 (9.5)	9.1(1.9)	26.0(5.8)
III BOQ 5812315 30 mg	59.9 (9.5)	7.9(2.0)	23.1(3.2)
IV Phenobarbital sodium	74.0(30.1)	16.3(3.3)	35.1(7.6)

D. DISCUSSION:

In this study there was no evidence of induction of the liver microsomal enzymes aminopyrine-N-demethylase, p-nitroanisole-O-demethylase or cytochrome P-450 as a result of 5-day oral exposure to 15 or 30 mg/kg/day of propoxur. There was no evidence that exposure to the test material resulted in an absolute or relative change in liver weights.

However, because the test material could have been given at a higher dosage level if mixed with the diet, the study is classified as supplementary.