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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Propoxur, Toxicology Chapter of the Registration Standard

MAY 18 1987

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Registration Division (TS-767C)

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Attached is the Toxicology Chapter of the Registration Standard for Propoxur.

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Toxicology Chapter
of the
Propoxur
Registration Standard

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TOXICOLOGY CHAPTER

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A. Toxicology Summary

Propoxur (O-isopropoxyphenyl methylcarbamate, also known as Baygon, Bay 39007, Unden, Sendran and Blattanex) is a component of a considerable number of registered products. Registered uses of these products include as household roach and ant sprays, flea and tick control agents for dogs and cats, crack and crevice treatments in food preparation areas, control of insects in dairy barns, and in sprays and/or foggers for control of adult mosquitos. Overall, there is considerable potential for at least incidental human and domestic animal exposure. However, no permanent tolerances have been issued for Propoxur in agricultural commodities.

Structurally, Propoxur is a carbamate, and its mechanism of acute toxicity involves temporary (reversible) cholinesterase inhibition. Orally, technical Propoxur is extremely toxic with reported oral LD_{50} values of 69 and 47 mg/kg for male and female rats respectively. The value for females places the technical material in toxicity category I by this exposure route. In a published study (Bull. World Health Org. 44: 241-249, 1971) which utilized human volunteers, a single oral dose of 1.5 mg/kg in a 42-year old human male reduced RBC cholinesterase activity to 27% of preexposure levels in 15 minutes. This was accompanied by a rise in blood pressure from 135/90 to 175/95, pronounced nausea and vomiting and profuse sweating 30-45 minutes after ingestion, with full recovery 2 hours after dosage. A single dose of 0.36 mg/kg resulted in a 43% drop in RBC cholinesterase activity, blurred vision, facial redness, sweating and stomach discomfort, but with rapid recovery. Five doses (30 minutes apart) of 0.15 or 0.2 mg/kg resulted in 40% RBC cholinesterase inhibition, but no symptoms.

The Agency is not aware of any studies which adequately define the dermal toxicity or inhalation toxicity potentials of technical Propoxur.

The dermal and eye irritation potentials of technical Propoxur are low (toxicity category IV). In an acceptable study utilizing the guinea pig maximization protocol of Magnussen and Kligman there were no indications of any dermal sensitization potential.

Although Propoxur is a cholinesterase inhibitor, it is a carbamate rather than an organophosphate, and so, by structural considerations, would not be expected to cause the classical form of delayed neurotoxicity associated with reaction with Neurotoxic Target Esterase (NTE).

The Agency does not have any acceptable subchronic toxicity data on Propoxur. Based on the incidental dermal exposure potential of most products containing Propoxur, a 21-day repeated dose dermal toxicity study would be required.

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However, there are some formulations used for flea and/or tick control on dogs and cats with (in addition to domestic animal dermal exposure) potential for human dermal exposure, both from treating the pet (particularly with dips) as well as subsequent normal contact with the animal. Because of these uses of Propoxur a 90-day subchronic dermal toxicity study is required. An acceptable 90-day study would also satisfy the 21-day repeated dose dermal requirement.

While there are no indications that Propoxur can cause teratogenic effects (although fetotoxicity does occur at a sufficiently high dose level), the two studies which the Agency has on file have been found to be deficient in a number of respects and merit only a supplementary classification.

In a 12-month dog feeding study currently classified as supplementary a NOEL was not observed as lowest-dose (200 ppm) dogs showed significantly elevated mean plasma cholesterol levels at 13, 26 and 52 weeks relative to their controls, and these elevations were part of dose-related trends. At 600 ppm there was increased mean liver weight and mean N-demethylase activity. There was a 100% incidence of atrophy of the thymus in high-dose dogs (1800 ppm through week 40; 3600 ppm through week 44; then 5400 ppm through week 52). Two of 6 males in the 600 ppm group showed somewhat reduced mean thymus weights, but histopathology was not done on this group.

A NOEL of 200 ppm was observed in an acceptable 106-week rat feeding study, with an LEL (weight depression in both sexes, increased incidence of hyperplasia of the bladder, and possibly a slight increase in neuropathy of the sciatic nerve) at 1000 ppm. At 5000 ppm these effects were more pronounced, and there was reduced food consumption, an increased incidence of muscular atrophy, and females consistently had lower mean plasma cholinesterase activity than their controls and the two lower dose groups; Additionally, there was a highly significant ($p < 0.0001$) increased incidence of bladder tumors for both sexes (correlating with the increased incidence of hyperplasia in this organ). Females at 5000 ppm had an increase of borderline significance ($p = 0.055$) in the incidence of uterine carcinoma.

There is an acceptable 2-year mouse oncogenicity study in which there was no evidence of tumorigenic effects at dietary dosage levels of up to 6000 ppm.

From these studies Propoxur has been classified as a B_2 (probable human) oncogen. Although neoplasias occurred only in one species there was an unusually high incidence (67-75%) in both sexes at the highest dose (vs. 0% in controls), bladder tumors are relatively rare in this species, there

was an early onset of hyperplasia and papillomas of the bladder, and the occurrence of bladder tumors in rats is somewhat uncommon in the absence of crystalline deposits.

The potency estimate Q* of Propoxur has been calculated to be 7.9×10^{-3} $(mg/kg/day)^{-1}$ in human equivalents, based upon the geometric mean of male and female bladder tumors (carcinomas and papillomas) in rats.

In the Peer Review Document for Baygon (September 4, 1986) it was stated that the registrant should be asked to provide a complete battery of mutagenicity tests.

In the acceptable mutagenicity studies which have been reviewed there are no indications of any activity associated with Propoxur. However, there exist several data gaps (including an in vitro specific locus study using a mammalian cell line, an in vitro unscheduled DNA synthesis or UDS study, a mammalian cell transformation study, and a DNA alkylation study) which should more adequately define the mutagenic potential (or lack thereof) for Propoxur.

Although some metabolism studies have identified many of the metabolites (including 2-isopropoxyphenol, 2-hydroxyphenyl N-methylcarbamate and 2-isopropoxy-5-hydroxyphenyl N-methylcarbamate), there exist a number of data gaps (including determination of distribution of material in different organs following single doses of radiolabeled test material), and a more precise quantitation as to how much Propoxur (and/or its metabolites) is excreted in feces, urine and/or respiration following dosage.

B. Toxicology Profile

81 Series: Acute toxicity and irritation

81-1: Acute oral toxicity

Sufficient data are available to demonstrate that technical Propoxur is in toxicity category I by the oral exposure route. In an oral intubation study (MRID 149030) using Wistar albino rats, technical (98.6%) Propoxur, administered as a solution in polyethylene glycol 400, was determined to have oral LD_{50} values (with 95% confidence limits) of 69 (60-79) mg/kg in fasted males and 47 (42-53) mg/kg in females. Rats receiving doses as low as 5 mg/kg showed temporary apathy; at higher doses symptoms included convulsions and tremors for several hours, typical of short-term (reversible) cholinesterase inhibition. The lowest dose level at which mortality occurred was 40 mg/kg.

81-2: Acute dermal toxicity

There is no dermal toxicity study available adequately defining the toxicity of technical Propoxur by this exposure route. A study is required.

81-3: Acute inhalation toxicity

There are no data available adequately defining the acute inhalation toxicity of technical Propoxur. A study is required.

81-4: Primary eye irritation

Sufficient data are available to demonstrate that technical Propoxur is in toxicity category IV by this exposure route. In one study (MRID 149034) administration of technical Propoxur to rabbit eyes resulted in some being scored "1" (but no higher than this) for conjunctival redness at 24 hours, with no other signs of irritation. According to the Subdivision F Hazard Evaluation Guidelines a score of 2 or more for conjunctival redness indicates a positive effect. In a second study (MRID 45097) administration of technical Propoxur to rabbit eyes resulted in no eye irritation at 24, 48 and 72 hours.

81-5: Primary dermal irritation

Sufficient data are available to show that technical Propoxur is in toxicity category IV by this exposure route. In one study (MRID 149034) with 24-hour occluded dermal exposure to technical Propoxur, a group of New Zealand white rabbits had scores of zero for both erythema and edema at 24 and 72 hours. In a second study (MRID 45097) there was no irritation following 24-hour occluded exposure to 500 mg doses of Propoxur which had been applied to the skin sites in acetone solution.

81-6: Dermal sensitization

Sufficient data are available to indicate a low dermal sensitization potential exists for technical Propoxur. In a study (MRID 141139) utilizing a maximization protocol no indication of dermal sensitization was elicited in a group of male guinea pigs.

81-7: Acute delayed neurotoxicity

No data are available. Although Propoxur is a cholinesterase inhibitor, it is a carbamate rather than an organophosphate, and so would not be expected to cause the classical form of delayed neurotoxicity associated with reaction with Neurotoxic Target Esterase (NTE). An acute delayed neurotoxicity study on hens is therefore not required. However, since neuropathy was noted in a 106-week chronic rat feeding study (MRID 142725) an acute study utilizing this species is required. This study should utilize appropriate histological techniques for determination of effects on nervous tissue. The registrant should consult with the Agency on protocols before undertaking this study.

82 Series: Subchronic Testing

82-1: Subchronic oral

Rodent:

No data are available. However, since the Agency has an adequate chronic 2-year rat feeding study, a 90-day subchronic rodent feeding study is not required.

Non-rodent:

No data are available. As long as a chronic (one year or more) dog feeding study is submitted, a 90-day subchronic non-rodent feeding study is not required.

82-2: 21-day repeated dose dermal toxicity:

No data are available. Based on potential dermal exposure to most household products containing Propoxur, where exposure is incidental (not purposeful), this study would be required in the absence of an acceptable 90-day subchronic dermal toxicity study (but see below).

82-3: 90-day subchronic dermal toxicity:

No data are available. While most uses of Propoxur involve only incidental dermal exposure, there are a number of flea and/or tick control products (dips and collars) registered for use on cats and/or dogs. In addition to the domestic animal dermal exposure, there is considerable potential for human exposure via the same route, both by normal contact with a pet as well as use of dip solutions. A 90-day subchronic dermal toxicity study is required to support these uses. An acceptable 90-day study would also satisfy the 21-day repeated dose dermal requirement.

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82-4: 90-day subchronic inhalation toxicity:

This study is required if use(s) may result in repeated inhalation exposure at a concentration likely to be toxic. Whether or not this study is required depends on the findings of the acute inhalation toxicity study and an exposure assessment.

82-5: 90-day subchronic neurotoxicity:

Chickens:

While Propoxur is a cholinesterase inhibitor, it is a carbamate, rather than an organophosphate. A 90-day subchronic neurotoxicity study on hens is therefore not required.

Mammalian:

A 90-day mammalian neurotoxicity study is normally required if neuropathy and/or neurotoxicity occur in acute oral, dermal or inhalation studies. If neuropathy is noted in the acute delayed neurotoxicity study (81-7) then a subchronic study on rats utilizing appropriate histological techniques for determination of effects on nervous tissues would be required. If such a study is necessary, the registrant should consult with the Agency on protocols.

<u>83 Series: Chronic and Long-term Studies</u>:

83-1: Chronic feeding

Rodent (rat):

Sufficient data are available. In a 106-week rat feeding study with 50 rats/sex/dose level (an additional 10 animals sex/dose level were sacrificed at one year) and dietary levels of 0, 200, 1000 and 5000 ppm (MRID 00142725) the NOEL was 200 ppm, and the LEL (weight depression - usually not statistically significant but part of a dose-related trend in both sexes, increased incidence of hyperplasia of the bladder, possibly a slight increase in neuropathy of the sciatic nerve) was 1000 ppm. At 5000 ppm these effects were more pronounced, along with reduced food consumption. Females at 5000 ppm consistently had lower mean plasma cholinesterase activity than their controls and the two lower dose groups.

Non-rodent (dog):

There is a 12-month dog feeding study (MRID 149040) which is currently classified as supplementary. A NOEL was not observed in this study as the lowest-dose (200 ppm) dogs showed

significantly elevated mean plasma cholesterol levels at 13, 26 and 52 weeks relative to their controls, and these elevations were part of dose-related trends. Additionally, there was a 100% incidence of atrophy of the thymus in high-dose dogs (1800 ppm through week 40; 3600 ppm through week 44; then 5400 ppm through week 52). Two of 6 males in the median (600 ppm) group showed somewhat reduced mean thymus weights, but histopathology was not done on this group. Other effects noted at 600 ppm were increased mean liver weight and mean N-demethylase activity.

The classification of this study has to be upgraded, or a new study has to be submitted.

83-2: Oncogenicity

Mouse:

Sufficient data are available. In a mouse oncogenicity study (MRID 100546) in which 50 mice/sex/dosage level were fed dietary concentrations of 0, 700, 2000 or 6000 ppm (an additional 10 mice/sex/dosage level were sacrificed at 6 months) there was no evidence for tumorigenic effects as a result of 2-year exposure.

Rat:

Sufficient data are available. In the 106-week rat study that satisfies the rodent chronic feeding study requirement (MRID 142725) 50 rats/sex were fed dietary levels of 0, 200, 1000 and 5000 ppm Propoxur (an additional 10 rats/ sex/dose were sacrificed after one year) more than 50% of the animals at the highest dose (5000 ppm) had developed papillomas or carcinomas of the urinary bladder after two years. Females at 5000 ppm also had an increased (borderline statistical significance) incidence of carcinoma of the uterus relative to their controls. A single male at 1000 ppm developed a papilloma of the bladder, and there was an increased incidence of hyperplasia of the epithelium of the bladder (a possible preneoplastic lesion) in both sexes at this dosage level. There was no evidence of any oncogenic or preneoplastic effects at 200 ppm.

83-3: Teratogenicity

Insufficient data are available. Two studies are on file and have been reviewed.

In a rat study (MRID 45094) technical Propoxur was mixed in the diet and fed to rats at 0, 1000, 3000 and 10,000 ppm. This is an older study (report date: 11/16/70), with only 10 dams/dosage level. In 1000 ppm rats there were decreased mean body weight gains for the dams and reduced mean fetal

weights; although differences were not statistically significant with respect to control values, they nevertheless were part of well-defined dose-related trends (at 3000 and 10,000 ppm these effects were more pronounced and were statistically significant). NOEL's for both maternal and fetal toxicity were therefore not observed. This rat teratology study is not acceptable, and must be redone.

In a rabbit study (MRID 100547) technical Propoxur was given at doses of up to 10 mg/kg/day. While no teratogenic and/or fetotoxic effects were noted, no pharmacologic effects were observed in the dams at any dose level. The review conclusion was that the study should be repeated using higher doses. In the repeat study it should be demonstrated that the highest exposure level is a maximally tolerated dose (MTD) or is reasonably close to it.

83-4: Reproduction

In a 3-generation rat reproduction study (MRID 55142) rats were fed 0, 250, 750, 2000 or 6000 ppm Propoxur in their diet. This is an older study (report date: 5/15/68), and it was noted in the original toxicology review that "The value of this study is restricted since BAY 39007 was not fed during the mating period, pregnancy, littering, and raising period for the young rats." This comment remains valid.

A 2-generation reproduction study is required.

84 Series: Mutagenicity:

As part of the recommendations in the Peer Review Document (September 4, 1986) for Baygon it was stated that the registrant should be asked to provide a complete battery of mutagenicity tests.

84-2(1): Gene mutation tests

(i) Microorganisms

(A) Bacteria, reverse mutation:

Salmonella typhimurium (Ames' assay)

In two acceptable studies no mutagenic activity was observed with or without S9 (rat) activation.

The first of these studies (BBPR01) involved replicate testing at doses of up to 12,500 ug/plate. At the highest dosage level there was cytotoxicity in all strains of S. typhimurium

used.

In the second study (MRID 149043) there was replicate testing at doses of up to 25,000 ug/plate, with sufficient cytotoxicity at high dose levels for all strains of S. typhimurium used. Also, a tryptophan-requiring strain of E. coli (WP2 hcr) was tested, with negative results.

(B) Eucaryotic microorganisms, forward and reverse mutations:

As dietary exposure to Propoxur has been demonstrated to cause bladder tumors in rats, this type of study is superseded by the requirement for one utilizing a mammalian cell line.

(ii) Submammalian organisms, sex-linked recessive lethal:

This type of study is also superseded by the requirement for one utilizing a mammalian cell line.

(iii) In vitro mammalian cell studies:

The Agency has no record that any acceptable studies have been submitted assaying for forward or reverse mutagenicity at specific loci in any of the appropriate mammalian cell lines. An in vitro specific locus mammalian cell study is required.

84-2(2): Structural chromosome aberration tests

(i) Eucaryotic microorganisms:
(ii) Submammalian organisms, chromosome tests:

No acceptable studies have been submitted for either of these two assay types. However, since oncogenicity has been demonstrated for technical Propoxur (or one of its metabolites) in the rat, it is more appropriate to directly test mammalian species and/or cell lines (see below), and these assays are therefore superseded.

(iii) Mammalian cells in culture:

Either a sister chromatid exchange or cytogenetic analysis study is required.

(iv) In vivo testing - mammals:

In an acceptable in vivo micronucleus assay (MRID 149041) in mice no mutagenic effect was noted at doses of up to 20 mg/kg.

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This study satisfies an in vivo mammalian testing requirement.

84-3: Tests for other genotoxic effects:

(i) DNA damage and repair:

Although Propoxur has been demonstrated to be oncogenic in rats, there is no information defining its potential for causing DNA damage in mammalian cells. An in vitro unscheduled DNA synthesis (UDS) study is therefore required.

(ii) Numerical chromosomal aberrations:

This study requirement is partially satisfied by the in vivo micronucleus assay (MRID 149041) which has been submitted. An additional in vitro study should be conducted.

(iii) Mammalian cell transformation

This study, utilizing cells in culture, should be conducted.

(iv) Target organ/cell analysis:

Studies should be conducted to determine whether Propoxur causes DNA synthesis inhibition, and whether DNA alkylation occurs as a result of exposure to either Propoxur and/or its metabolites.

85 Series:

85-1: Metabolism

Short-term (MRD 121197) and subchronic (MRID 142731) oral exposure studies have been submitted which sufficiently identify a number of metabolites (such as O-isopropoxyphenyl and 2-hydroxyphenyl methylcarbamate) which are rapidly excreted in urine following exposure to Propoxur. However, the Agency has insufficient information regarding possible bioaccumulation and/or bioretention of either Propoxur or its metabolites. A study (preferably using the protocol outlined in the Section F Guidelines for a metabolism study) should be conducted.

85-2: Domestic animal safety testing

Although Propoxur-containing products are registered for use on both dogs and cats, they involve application of formulations which may contain other actives or which may contain inerts affecting dosage rates or otherwise modifying toxicity. Because of this the Agency has required (and will continue to do so) studies on these proposed formulated products.

85-3: Dermal absorption

The data regarding the dermal absorption potential of Propoxur are insufficient. Since human exposure potential exists, a study is required.

C. Data Gaps

The following is a summarization of the data gaps which exist for technical Propoxur:

81-2: Acute dermal toxicity

81-3: Acute inhalation toxicity

81-7: Acute delayed neurotoxicity - rat

82-2: 21-day repeated dose dermal toxicity:
Note: this study requirement would be satisfied by a 90-day subchronic dermal study (see 82-3, below).

82-3: 90-day subchronic dermal toxicity:
This study is required to support the registration of Propoxur-containing products which are applied to domestic animals.

82-4: 90-day subchronic inhalation toxicity (this may be required based on the findings of the acute inhalation LC_{50} study and an exposure assessment).

82-5: 90-day subchronic rat neurotoxicity if there are positive findings in the rat acute delayed neurotoxicity study.

83-1: Chronic feeding (dog) (a NOEL is required)

83-3: Teratogenicity (two species, rodent and non-rodent)

83-4: Reproduction

84-2(1): Gene mutation test (iii) in vitro specific locus study using a mammalian cell line

84-2(2): Structural chromosome aberration tests (iii) Mammalian cells in culture. Either a sister chromatid exchange study or cytogenetic analysis study is required.

84-3: Tests for other genotoxic effects: (i) DNA damage and repair: an in vitro unscheduled DNA synthesis (UDS) study is required.

84-3: Tests for other genotoxic effects: (ii) Numerical chromosomal aberrations: a study other than an in vivo micronucleus assay should be conducted.

84-3: Tests for other genotoxic effects: (iii) Mammalian cell transformation: a study utilizing an appropriate cell line in culture should be conducted.

84-3: Tests for other genotoxic effects: (iv) Target organ/cell analysis: Studies should be conducted to determine whether Propoxur causes DNA synthesis inhibition, and whether DNA alkylation occurs as a result of exposure to either Propoxur or its metabolites.

85-1: Metabolism (preferably using rats) measuring bioaccumulation and/or bioretention of either Propoxur or its metabolites is required.

85-3: Dermal absorption

D. Tolerance and Tolerance Reassessment

There exist no approved tolerances for Propoxur on any agricultural commodities. However, Propoxur-containing formulations are registered as mosquito adulticides, and this use does result in residues on some crops. This particular issue has to be satisfactorily resolved, particularly in view of the B_2 oncogenic classification of Propoxur.

The Office of Pesticide Programs has set a reference oral dose for Propoxur of 0.004 mg/kg, applying a safety margin of approximately 100 to a dosage (0.36 mg/kg) causing short-term effects (43% RBC cholinesterase inhibition, blurred vision, facial redness, sweating and stomach discomfort) after ingestion by a human volunteer.

E. Toxicological Issues

One issue involves quantitation of the risk associated with human exposure to Propoxur. The potency estimate, Q* has been calculated as 7.9×10^{-3} $(mg/kg/day)^{-1}$ in human equivalents, based upon the incidence of male and female bladder tumors (carcinomas and papillomas) in a 2-year rat study. Some of the data which has been requested in this chapter (such as dermal absorption) has a direct relevance to a quantitative risk assessment for this active.

Additional mutagenic studies are necessary to give some possible insight into the mechanism(s) of oncogenicity of Propoxur.

The teratogenic and fetotoxic NOELs and LELs for Propoxur should be more precisely defined, as should be the NOEL for a chronic dog study.

F. Toxicology Summary Tables

GENERIC DATA REQUIREMENTS FOR PROPOXUR

Data Requirement	Composition	1/ Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Acute Oral - Rat	TGAI	B, D, G, H, I, P	YES	MRID 149030	NO
81-2 - Acute Dermal	TGAI	B, D, G, H, I, P	NO		YES
81-3 - Acute Inhalation - Rat	TGAI	B, D, G, H, I, P	NO		YES(3)
81-4 - Eye Irritation - Rabbit	TGAI	B, D, G, H, I, P	YES	MRID 149034, MRID 45097	NO
81-5 - Dermal Irritation - Rabbit	TGAI	B, D, G, H, I, P	YES	MRID 149034, MRID 45097	NO
81-6 - Dermal Sensitization - Guinea pig	TGAI	B, D, G, H, I, P	YES	MRID 141139	NO
81-7 - Acute Delayed Neurotoxicity - Rat	TGAI	B, D, G, H, I, P	NO		YES(4)
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding - Rodent, Non-rodent	TGAI		NO		NO

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GENERIC DATA REQUIREMENTS FOR PROPOXUR

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 2/
§158.135 Toxicology (Cont.)					
82-2 - 21-Day Dermal	TGAI	B, D, G, H, I	NO		YES(5)
82-3 - 90-Day Dermal	TGAI	P	NO		YES(6)
82-4 - 90-Day Inhalation - Rat	TGAI	-	NO		PERHAPS(7)
82-5 - 90-Day Neurotoxicity- Hen/Mammal (continued)	TGAI	B, D, G. H, I, P	NO		PERHAPS(8)
CHRONIC TESTING:					
83-1 - Chronic Toxicity - Rodent	TGAI	B, D, G, H, I, P	YES	MRID 142725	NO
Non-rodent	TGAI	B, D, G, H, I, P	NO		YES(9)
83-2 - Oncogenicity Study - 2 species: Rat and Mouse preferred	TGAI	B, D, G, H, I, P	YES	MRID 100546, MRID 142725,	NO
83-3 - Teratogenicity - 2 species	TGAI	B, D, G, H, I, P	NO		YES
83-4 - Reproduction, 2-generation	TGAI	B, D, G, H, I, P	NO		YES

GENERIC DATA REQUIREMENTS FOR PROPOXUR

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (continued)					
MUTAGENICITY TESTING					
84-2-1 Gene Mutation	TGAI	B, D, G, H, I, P	PARTIALLY	MRID 149043, BBPR01	YES(10)
84-2-2 Chromosomal Aberration	TGAI	B, D, G, H, I, P	NO		YES(10)
84-3 - Other Mechanisms of Mutagenicity	TGAI	B, D, G, H, I, P	PARTIALLY	MRID 149041	YES(10)
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	B, D, G, H, I, P	PARTIALLY	MRID 121197, MRID 142731	YES(11)
85-2 - Domestic Animal Safety	Choice	P	NO		NO
85-3 - Dermal Absorption	PAIRA	B, D, G, H, I, P	NO		YES

1/ Composition: PAI = Pure active ingredient; PAIRA = Pure active ingredient, radiolabelled; Choice = Choice of several test substances determined on a case-by-case basis.
2/ The use patterns are coded as follows: B=Terrestrial, Non-Food; D=Aquatic, Non-food; G=Forestry; H=Domestic Outdoor; I=Indoor; P=Applied to pets
3/ Study or studies are required to support registrations of Propoxur-containing products involving spray application, or which produce a respirable vapor or aerosol.
4/ The Registrant should consult with the Agency on protocols before undertaking this study.
5/ The 21-day dermal study requirement would be satisfied by a 90-day dermal study.
6/ The study is required to support registration of products used for pet flea and tick control; this study could also be used in lieu of the 21-day dermal study requirement for other products.
7/ Whether or not this study is required depends on the findings of the acute inhalation toxicity study and an exposure assessment.
8/ This study is required if neuropathy and/or neurotoxicity are noted in the acute neurotoxicity study. The registrant should consult with the Agency on protocols before undertaking this study.
9/ The classification of the study in MRID 149040 has to be upgraded, or a new study has to be submitted.
10/ At least one *in vitro* mammalian cell study is required.
11/ Information should be submitted regarding bioaccumulation and/or bioretention of Propoxur and its metabolites.

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G. BIBLIOGRAPHY - page 1

00149030 Heimann, K. (1982) Carbamate UN, Technical: Study for Acute Toxicity on Rats: Report No. 11329. Unpublished Mobay Report No. 82740 prepared by Bayer AG. 8 p.

00149034 Thyssen, J.; Lorke, D. (1978) Propoxur: Studies on the Irritant Effect on Skin and Mucous Membrane [(Eyes): Rabbits]: 82-T-163. Unpublished Mobay Report No. 82229 prepared by Bayer AG. 5 p.

00045097 Crawford, C. R.; Anderson, R. H. (1971) The Skin and Eye Irritating Properties of ®Baygon Technical and Baygon 70% WP to Rabbits: Report No. 29706. (Unpublished study received Aug. 16, 1972 under 2F1244; submitted by Chemagro Corp., Kansas City, Mo.; CDL:091768-AF)

00141139 Heimann, K. (1982) Propoxur (The Active Ingredient of Baygon® and Unden®): Study of Sensitization Effect on Guinea Pigs: Bayer Report No: 11218. Unpublished Mobay report 82567 prepared by Bayer AG Institut fuer Toxikologie. 11 p.

00142725 Suberg, H.; and Loeser, E. (1984) Chronic Toxicological Study with Rats (Feeding Study over 106 Weeks): Report No. 12870. Unpublished Mobay Study No. 88501 prepared by Bayer Institute of Toxicology.

00149040 Hoffmann, K.; Groning, P. (1984) BOQ 58 123 15, C.N. Propoxur): Chronic Toxicity to Dogs on Oral Administration (12-month Feeding Study): Report No. 12605. Unpublished Mobay Report No. 86665 prepared by Bayer AG. 240 p.

00100546 Bomhard, E.; Loeser, E.; Frank; et al. (1981) BOE 5812315 (Propoxur, the Active Ingredient of Baygon®): Chronic Toxicity Study on Mice (2-year Feeding Experiment): Bayer Report No. 9954; 69686. (Unpublished study received May 3, 1982 under 2F1244; prepared by Bayer, AG, West Germany, submitted by Mobay Chemical Corp., Kansas City, MO; CDL:070831-A)

00045094 Lorke, D. (1971) Bay 39007--Examinations for Embryotoxic Effects among Rats: Pharma Report No. 2388; Report No. 29035. (Unpublished study received Aug. 16, 1972 under 2F1244; prepared by Farbenfabriken Bayer, AG, submitted by Chemagro Corp., Kansas City, Mo.; CDL:091768-AC)

00100547 Schlueter, G.; Lorke, D. (1981) BOE 5812315 (Propoxur, the Active Ingredient in Baygon®) Study of Embryotoxic and Teratogenic Effects on Rabbits after Oral Administration: Bayer Report No. 10183; Mobay ACD Report No. 80034. (Unpublished study received May 3, 1982 under 2F1244; prepared by Bayer, AG, West Germany, submitted by Mobay Chemical Corp., Kansas City, MO; CDL:070831-B).

00055142 Löser, E.; Lorke, ? (1973) Bay 39007 Generation Studies on Rats: Report No. 798; Report No. 23299. Rev. (Translation from German; unpublished study received Oct 1, 1974 under 3125-306; prepared by Farbenfabriken Bayer, AG, W. Germany, submitted by Mobay Chemical Corp., Kansas City, Mo.; CDL: 140168-J)

00149043 Ohta, T.; Moriya, M. (1983) Propoxur: Microbial Mutagenicity Study. Unpublished study prepared by Institute of Environmental Toxicology. 7 p.

00149041 Herbold, B. (1980) Micronucleus Test on Mouse To Evaluate BOE 5812315 for Mutagenic Potential: BOE 5812315: Report No. 9274. Unpublished Mobay Report No. 69317 prepared by Bayer AG. 17 p.

00121197 Everett, L. J.; Gronberg, R. E. (1971) The Metabolic Fate of ®BAYGON (o-Isopropoxyphenyl methylcarbamate) in the Rat. Report no. 28797. Unpublished study prepared by Chemagro Corporation Research & Development Department.

00142731 Eben, A.; Karl, W.; Machem, L. (1984) Studies on the Biotransformation of Propoxur in the Rat: Report No. 12866. Unpublished Mobay Study No. 88584 prepared by Bayer Institute of Toxicology. 49 p.

BBPR01 Herbold, B. Salmonella/microsome test to evaluate for point mutation. Bayer AG Institute of Toxicology. Report no. 11301, dated June 12, 1982. In Acc. 256151.

Tox Chem No. 508 - Propoxur, Baygon | File Last Updated _____ | Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology - rabbit; Bayer A.G. Institut Fuer Toxikologie; #10183; 9/9/81	Technical BOE 5812315 99.6%	070831 MRID100547	Levels tested - 0, 1, 3 and 10 mg/kg/day. Teratogenic NOEL >10 mg/kg/day (HDT) Maternal NOEL >10 mg/kg/day (HDT) Fetotoxic NOEL >10 mg/kg/day (HDT) Himalayan rabbits CHBB: HM strain used.		Minimum 002156 Supplementary XXXXXX
Teratology - rat; Bayer AG Institute of Toxicology; report no. 2388; 11/16/70	Technical Proproxur 98.4%	091768 MRID 45094	Levels tested: 0, 1000, 3000 and 10,000 ppm. Original review stated that maternal and fetotoxic NOELs were at 1000 ppm; however, a re-evaluation shows that mean maternal weight gain and mean fetal weights for 1000 ppm animals were lower than their controls, although not necessarily significantly so (but part of dose-related trends). At 3000 and 10000 ppm there were definite maternal (significant body weight gain depression, lower food consumptions) and fetotoxic (significant mean weight depression) effects.		003692 Supplementary XXXXXX
3-Generation reproduction-rat; Bayer AG Institute of Toxicology; report no. 798; 9/27/68	Bay 39007 technical 98.4%	091768 MRID 55142	Dosage levels: 0, 250, 750, 2000 and 6000 ppm in FB30 rats. Reproduction NOEL = 250 ppm; LEL = 750 ppm (decreased pup number); however, value of study is limited because "Except for the mating period, pregnancy, littering, and the raising period for the young rats, the animals were treated with BAY 39007 during the entire testing time."		003692 003712 Supplementary XXXXXX

Tox Chem No. 508 - Propoxur, Baygon File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
2-year feeding/oncogenicity-mice; Bayer AG Institute Fuer Toxicologie; #9954; 5/12/82	BOE 5812315 99.6%(wks 1-6) BOE 5812315 90% (remainder of study)	070831 MRID100546	Levels tested - 0, 700, 2000 and 6000 ppm. Oncogenic NOEL >6000 ppm (HDT). Systemic NOEL = 700 ppm. LEL = 2000 ppm (increase in survival time in both sexes and decreased male weight gain).		Minimum 002156 Minimum XXXXXX
2-year feeding/oncogenic - rat; Wuppertal Elberfeld; #12870, 09/20/84	Technical 99.4%	255177 MRID142725	Oncogenic NOEL = 200 ppm. Oncogenic LEL = 1000 ppm (bladder papilloma in 1/50 males). At 5000 ppm 25/49 males and 28/48 females had bladder papillomas. At 5000 ppm carcinoma of the bladder in 8/49 males and 5/48 females; females at 5000 ppm also had an increased incidence of uterine carcinoma (8/48) as compared to their controls.		Minimum (oncogenicity) 004231 XXXXXX
			Systemic NOEL = 200 ppm. Systemic LEL = 1000 ppm. Effects in both sexes included weight depression, increased incidence of urothelial hyperplasia of the bladder, slight increase in neuropathy. At 5000 ppm (both sexes) significant (usually $p < 0.01$) weight depression; less food consumption; increased incidence and degree of neuropathy; more splenic atrophy. 41/49 males and 48/48 females had urothelial hyperplasia of the bladder. Males only showed increased thromboplastin time at 24 months. Females at 5000 ppm consistently had lower mean plasma than controls and two lower exposure groups. Levels tested: 0, 200, 1000 & 5000 ppm (dietary).		Supplementary (feeding) 004231 Minimum 005359 XXXXXX

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Tox Chem No. 508 - Propoxur, Baygon File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
12-Month feeding - dog; Bayer AG Institute of Toxicology; 12605; 04/11/84	Propoxur 99.4%	256151 MRID149040	Controls (0 ppm), 200 ppm, 600 ppm and high-dose (1800 ppm thru wk 40, then 3600 ppm thru wk 44, then 5400 ppm thru wk 52). NOEL was not observed as there was significantly elevated plasma cholesterol in 200 ppm dogs at weeks 13, 26 and 52 wks relative to controls and these findings were part of dose-related trends. At 600 ppm there were significant increases in mean liver weight and mean N-demethylase activity. Symptoms of ChE inhibition were present in high-dose dogs after dietary level was raised to 5400 ppm.		Supplementary 005692 XXXXXX
Mutagenic - in vivo micronucleus (mouse); Bayer AG Institute of Toxicology; EHR File no. 2347; 6/27/80	Propoxur 99.2%	256151 MRID149041	No mutagenic effect was observed at doses of up to and including 2 x 10 mg/kg.		Acceptable 005692 XXXXXX
Mutagenic - Salmonella typhimurium reversion (Ames) study; Bayer AG Institute of Toxicology; Report no. 11301; 06/12/82	Carbamate UN technical 98.6%	256151	No mutagenic activity for the test material was observed with and w/o metabolic S9 (from rat livers) in replicate studies at doses of up to 12,500 ug/plate. At the highest level there was cytotoxicity in all strains of S. typhimurium used (TA 1535, TA 100, TA 1537, TA 98).		Acceptable 005692 XXXXXX

Tox Chem No. 508 - Propoxur, Baygon File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenic - Salmonella typhimurium and E. coli reversion (Ames assay), Institute of Toxicology (Japan); report no. 84124; 02/28/83	Propoxur 98%	256151 MRID149043	No mutagenic effect was observed for the test material w/wo S9(rat) activation in replicate doses of up to 25,000 ug/plate. There was sufficient cytotoxicity at 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 appropriate mutagenic responses.		Acceptable 005692 XXXXXX
Metabolism - rat; Wuppertal-Elberfeld; Report no. 12866; 08/17/84	Baygon (98.5-98.8%)	255177 MRID142731	The following metabolites were identified in urine of rats fed 8000 ppm Baygon for 13 weeks: M1 = 1,2-Dihyroxybenzene M2 = 2-Isopropoxyphenol M3 = 2-Hydroxyphenyl methylcarbamate M4 = 2-Isopropoxyphenyl-carbamic acid M5 = 2-Isopropoxyphenyl-hydroxy(-) methylcarbamate M6 = 2-Isopropoxy-5-hydroxyphenyl-carbamic acid M6 CII=2-Isopropoxy-5-hydroxyphenyl-carbamic acid M S 3 =2-Isopropoxy-5-hydroxyphenyl hydroxymethylcarbamate M7 = 1,5-Dihydroxy-2-isopropoxy-benzene		Supplementary 004231 Acceptable in identification of some metabolites, otherwise supplementary XXXXXX

Tox Chem No. 508 - Propoxur File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Metabolism - rat; Chemagro; #28797	^{14}C Baygon	094546 MRID121197	Within 16 hours, 60% excreted in urine (2-hydroxyphenyl-N-methylcarbamate and O-isopropoxyphenyl), 20-25% as volatile compounds and the remainder in feces. In total, 85% eliminated in 16 hrs.		003693 Acceptable in identification of some metabolites, otherwise supplementary XXXXXX
Acute oral LD_{50} - rat; Bayer AG Institute of Toxicology; #11329; 12/15/82	Carbamate UN 98.6%	256151 MRID149030	Oral LD_{50} (fasted M)=69(60-79) mg/kg Oral LD_{50} (fasted F)=47(42-53) mg/kg Unfasted M: 167(146-192) mg/kg Unfasted F: 96(87-106) mg/kg Cholinergic symptoms (convulsions, tremors, spastic gait, bristling coat, apathy) noted. No symptoms in fasted rats at 1 mg/kg or in unfasted rats at unfasted rats at 10 mg/kg.		Supplementary 005692 Minimum XXXXXX
Primary dermal irritation - rabbit; Bayer AG Institute of Toxicology #82229; 09/20/78	Propoxur technical 99.2%	256151 MRID149034	PDIS = 0.00 following 24-hr occluded exposure.	IV	Minimum 005692 XXXXXX
Primary eye irritation - rabbit; Bayer AG Institute of Toxicology; #82229; 09/20/78	Propoxur technical 99.2%	256151 MRID149034	Minimal (score of 1) conjunctival redness in 2/3 unwashed eyes at 24 hrs, clearing by 48 hrs.	IV	Minimum 005692 XXXXXX
Primary dermal irritation - rabbit; Chemagro Research; #29706;3/26/71	Technical 97.5%	091768 MRID 45097	No irritation following application of 500 mg to abraded or unabraded skin.	IV	003692 Minimum XXXXXX
Primary eye irritation-rabbit; Chemagro Research; #29706; 03/26/71	Technical 97.5%	091768 MRID 45097	No ocular irritation. Dose tested: 100 mg test substance.	IV	003692 Minimum XXXXXX

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Tox Chem No. 508 - Propoxur, Baygon File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Dermal sensitization - guinea pig; Bayer AG; T 8011718; 10/15/82	Technical 98.8%	253352 MRID141139	Not a sensitizer (maximization protocol)		Invalid 003852 Minimum 002772

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DATA EVALUATION REPORT COVER
FOR MRID 149030

Reviewed by: B. T. Backus, 12/16/86

Secondary reviewer: M. van Gemert M. van Gemert 5/15/87 Acc. 256151

CONCLUSIONS:

I reviewed this report in December, 1986. At that time I classified this study as core supplementary because of a lack of reporting of a considerable amount of data (including body weights and individual necropsy results). However, the comment was made at the time that "the rat oral LD_{50}'s reported in this study...can be accepted."

However, because the study adequately defines LD_{50} values (and mortality at each dose level is reported) and the symptoms which occurred are also given, the classification of this study can be upgraded to minimum.

Byron T. Backus 05/14/87

Byron T. Backus, Toxicologist
Review Section III
Toxicology Branch, HED

Reviewed by: Byron T. Backus 12/17/86 - ~~005692~~
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 005896

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

ACCESSION NUMBER: 256151 MRID NO.: ~~not given~~ 149030

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).

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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)

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MRID 149074

12 Marcia Gemert 12.11.86

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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): Thyssen, 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" 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. 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:

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

DATA EVALUATION REPORT VII 005896

STUDY TYPE: Primary eye 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): 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.

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

C. METHODS AND RESULTS:

1. Observations: According to the table on p. 5 the eyes were were examined at 24, 48 and 72 hrs (according to the text on p. 2 they were examined at 2, 48 and 74 hrs).

2. Results: All of the exposed eyes are reported (p. 5) as being negative for irritation at 24, 48 and 72 hrs.

D. DISCUSSION:

The results (no indications of primary eye irritation at 24 hrs and subsequently following insertion of 100 mg in the eye) indicate that technical propoxur has a low eye irritation potential (toxicity category IV).

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MRID 141139
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

005896

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Baygon (Propoxur); Dermal Sensitization in Guinea Pigs

TO: Jay Ellenberger (PM-12
Registration Division (TS-767)

8/24/84

FROM: Robert P. Zendzian PhD Acting Head
Review Section III
Toxicology Branch
HED (TS-769)

THROUGH: William Burnam, Chief
Toxicology Branch

8/25/84

Compound Baygon (propoxur) Registrant Mobay

Registration #3125-174 Accession #253352

Tox Chem #508

Action Requested

The registrant has submitted a dermal sensitization study of propoxur in the guinea pig for review.

Conclusion

The method has been identified as the guinea pig maximization test of Magnussen and Kligman an acceptable protocol for this purpose. The compound is not a sensitizer.

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Data Evaluation Report 005896

Compound Propoxur (Baygon®)

Citation

Propoxur (The Active Ingredient of Baygon® and Unden®) Study of Sensitization Effect on Guinea Pigs. K.G. Heimann, Bayer AG, Institut fuer Toxicologie, Study No T 8011718 Oct 15, 1982

Reviewed by [signature] 8/14/85
Robert P. Zendian PhD
Pharmacologist

Core Classification Minimum

Tox Catagory Not a sensitizer

Conclusion

The method has been identified as the guinea pig maximization test of Magnussen and Kligman an acceptable protocol for this purpose. The compound is not a sensitizer.

Materials

Propoxur, 2-(1-Methylethoxy)phenol methylcarbamate BOQ 5812315; Batch No. 234; Purity 98.8%

Male guinea pigs, Pirbright White W 58 form Winkelmann.

Methods

Animals were assigned randomly to a control and a treatment group of 15 animals each. The dermal area was clipped and remaining hair removed with a diplatory cream. After 24 hours each animal received 6 intradermal injections in pairs down the line of the back. Test animals were dosed as follows;

1st Injection Pair (head)
Freund's complete adjuvant, 1:1 in water.

2nd Injection pair (middle)
1% propoxur formulated with polyethylene glycol 400

3rd Injection pair (tail)
1% propoxur formulated with equal parts polyethylene glycol 400 and Freund's complete adjuvant, 1:1 in water.

The control group was dosed identically except that sites 2 and 3 did not receive propoxur.

Six days later the application sites were depilated and the site massaged with 10% sodium laural sulfate in vaseline. Twenty-four hours later filter paper saturated with either 2.5%

Reviewed by: Byron T. Backus Byron T. Backus 05/14/87
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D. Marcia van Gemert 5/14/87
Section 3, Tox. Branch (TS-769C)

005896

DATA EVALUATION REPORT II

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

ACCESSION NUMBER: 091768 MRID NO.: 45097

TEST MATERIAL: ®BAYGON Technical

SYNONYMS: Propoxur, 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): Report no. 29706

SPONSOR: Chemagro Corporation

TESTING FACILITY: Chemagro Corporation Research Department

TITLE OF REPORT: The Skin and Eye Irritating Properties of ®BAYGON Technical and BAYGON 70% WP to Rabbits

AUTHOR(S): Crawford, C. R. & Anderson, R. H.

REPORT ISSUED: 03/26/71

CLASSIFICATION: Core Minimum Data

CONCLUSIONS:

1. The results (negative for skin irritation at all sites - both intact and abraded - at 24 and 72 hours with a primary irritation score of 0 for all subjects) indicate the test material is in toxicity category IV in terms of its dermal irritation potential.

A. MATERIALS:

1. Test compound: ®Baygon technical, 97.5%, batch no. 9050556.

2. Test animals: Mature New Zealand type rabbits.

B. STUDY DESIGN:

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

2. Test material administration: "Technical material was dissolved in acetone and 500 mg applied to each abraded and unabraded area under a 1-inch square of gauze. A piece of rubber glove approximately 2 x 2 inches was placed over the compound to prevent the patch from shifting and to retard evaporation. The trunk of the animal was then wrapped... After 24 hours the wrapping was removed."

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

C. METHODS AND RESULTS:

1. Observations: The application sites were examined for erythema and edema at 24 hours (right after the wrapping was removed) and again at 72 hours.

2. Results: There was no indication of irritation at any abraded or intact site at 24 or 72 hrs. The average primary irritation score = 0.0.

D. DISCUSSION:

The results (average primary irritation score = 0.0 following 24-hr cccluded dermal exposure) indicate that technical Propoxur has a low dermal irritation potential (toxicity category IV).

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Reviewed by: Byron T. Backus Byron T. Backus 05/14/87
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) M. van Gemert 5/14/87

005896

DATA EVALUATION REPORT III

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

ACCESSION NUMBER: 091768 MRID NO.: 45097

TEST MATERIAL: ®BAYGON Technical

SYNONYMS: Propoxur, 2-isopropoxy-phenyl-N-methylcarbamate

STUDY NUMBER(S): Report no. 29706

SPONSOR: Chemagro Corporation

TESTING FACILITY: Chemagro Corporation Research Department

TITLE OF REPORT: The Skin and Eye Irritating Properties of ®BAYGON Technical and BAYGON 70% WP to Rabbits

AUTHOR(S): Crawford, C. R. & Anderson, R. H.

REPORT ISSUED: 03/26/71

CLASSIFICATION: Core Minimum Data

CONCLUSIONS:

1. The results (no ocular irritation was observed at any time in the 72 hrs following instillation of 100 mg of Baygon technical in rabbit eyes) indicate that technical Baygon is in toxicity category IV in terms of its eye irritation potential.

A. MATERIALS:

1. Test compound: ®Baygon technical, 97.5%, batch no. 9050556.

2. Test animals: Mature New Zealand type rabbits.

B. STUDY DESIGN:

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

2. Test material administration: "100 mg of technical material was placed in the left eye of 6 rabbits... After 24 hours the rabbits eyes were examined for obvious signs of irritation... One drop of 2% fluorescein sodium opthalmic solution was then dropped directly into the eye and the eye examined for injury to the cornea under ultraviolet light. Further observations were made at 48 and 74 hours."

propoxur formulated with polyethylene glycol 400 (test group) or the vehicle (control group) was applied to the injection sites for 24 hours, secured by an elastic adhesive bandage.

Three weeks after the intradermal injection all animals were challenged for 24 hours with a filter paper saturated with 1.2% propoxur formulation applied to the left site sites and a vehicle saturated filter paper applied to the right hand sites.

Twenty-four and 48 hours after removal of the challenge material the sites were examined and scored for reaction.

Results

No reactions were observed in the test group and one reaction in the control group.

83-1 (Non Rodent)
MRID 149040
005692

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Section 3, Tox. Branch (TS-769C) 12.17.84

005896

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.

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4. Besides findings present in lower dose groups (significant increases in mean liver weight, plasma cholesterol level, N-demethylase 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.

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.

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

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.

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): 005692

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

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

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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	Calcium*
X	Chloride*
	Magnesium*
	Phosphorous*
X	Potassium*
X	Sodium*

X	Enzymes
X	Alkaline phosphatase
	Creatinine phosphokinase*°
	Lactic acid dehydrogenase
X	Serum alanine aminotransferase (also SGPT)*
X	Serum aspartate aminotransferase (also SGOT)*
	gamma glutamyl transferase
X	glutamate dehydrogenase

X	Other:
	Albumin*
X	Blood creatinine*
X	Blood urea nitrogen*
X	Cholesterol*
	Globulins
X	Glucose*
X	Total Bilirubin*
X	Total Serum Protein*
	Triglycerides
X	Serum protein electrophoresis

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

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).

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Serum protein was usually significantly lower in high-dose dogs; from p. 37: 005692

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.

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	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	Digestive system	X	Cardiovasc./Hemat.	X	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-Thymus wt(g)	Thyroid-body wt ratio (g/kg)	Mean Thymus-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.

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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

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.

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.

CASWELL FILE
005896
005359

87-1 (RAT)
87-2 (RAT)
MRID 142725

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

AUG 18 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: NOEL for Baygon (Propoxur) in a 2-year rat chronic feeding study; comparison with a human volunteer study.

TO: Reto Engler, Ph.D., Chief
Mission Support Staff
Toxicology Branch, HED (TS-769C)

FROM: Byron T. Backus, Toxicologist
Review Section III
Toxicology Branch, HED (TS-769C)

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

M. van Gemert 8/14/86

and

Theodore M. Farber, Ph.D., Chief
Toxicology Branch, HED (TS-769C)

Background:

The question has arisen as to whether a slight (maximum 3.8%), but statistically significant (primarily during the first 20 weeks), mean body weight depression in male rats fed 200 ppm Baygon in their diet over a 2-year period was a toxicological effect of the test material. In a previous review (B. Backus, January 1985) it was stated that it was, and that a NOEL was therefore not observed. This is a reassessment of that statement, as well as a review of a human volunteer study from the literature.

Comments and Conclusions:

1. Baygon is a cholinesterase inhibitor, and females are usually more susceptible than males to the acute effects of pesticides of this type. However, mean body weights of 200 ppm females generally were within 2-3 grams of the corresponding control value for weighings during the first 40 weeks of the study. After that period, 200 ppm females actually tended to have slightly higher mean body weights than their controls (although differences were never statistically significant).

2. Significant differences between mean weights of 200 ppm males and their controls occurred almost exclusively in the first 20 weeks of the study, during a period when males in the 200 ppm group had a slightly (statistically not significant) lower mean food consumption than their controls, suggesting the possibility that the 200 ppm Baygon diet was less palatable than the regular diet. It is emphasized that, other than the equivocal weight depression, there was no other possible indication of toxicity.

3. From the above it is concluded that the mean body weight depression in 200 ppm males observed in the study was equivocal, and that 200 ppm was a toxicological NOEL.

4. In a report titled "Toxicity of Carbamates for Mammals" (Vandekar, Plestina & Wilhelm, 1971) an oral dose of 135 mg of Propoxur (1.5 mg/kg to a 90-kg human male) resulted in pronounced symptoms (pronounced nausea, vomiting, profuse sweating, a rise in blood pressure from 135/90 to 175/95) of cholinesterase inhibition 30-45 minutes after ingestion. There was a maximum of 73% RBC ChE activity depression 15 minutes after ingestion. According to the graph, RBC ChE had essentially recovered to normal at 2 hrs.

   Subsequently, an unspecified number of volunteers took 5 doses of either 0.15 or 0.2 mg/kg at half-hourly intervals. In each case a "symptomless depression" was observed in RBC ChE, to about 60% of normal.

   A dose of 1.5 mg/kg, while causing symptoms in a human volunteer when ingested all at once, was essentially "detoxified" (RBC ChE activity returned to normal) in 2 hours (according to an accompanying graph). At this rate of RBC ChE activity recovery a cumulative dose of 1.5 mg Baygon/kg over a 24 hr period would probably not have resulted in any evident symptoms; this would be equivalent to 60 ppm in the diet. However, 1.5 mg/kg x 12 (number of 2-hr periods in 24 hrs) = 18 mg/kg (720 ppm) would probably have caused symptoms.

   It is noted that 0.36 mg/kg is reported as having caused "short-lasting" effects with recovery of RBC ChE within 3 hours (note that detoxification of 1.5 mg/kg took place in approximately 2 hours; this may indicate individual variation or some other factors at work).

Data Evaluation Report (1)

004231

Compound:

2-isopropoxy-phenyl-N-methylcarbamate, BOQ 5812315, Propoxur, Baygon

005896

Study type:

2-year rat feeding and oncogenicity

Citation:

Suberg, H. and Löser, E. BOQ 5812315 (common name propoxur) chronic toxicological study with rats (Feeding study over 106 weeks). Report No. 12870, dated August 20, 1984. Studies conducted at Wuppertal-Elberfeld. Received at EPA 10-23-84; in Acc. 255177.

The report also contains the following:

Glaister, J.R. BOQ 5812315: 2 year carcinogenicity/chronic toxicity study in the rat histopathology report. HLE Report no. 3463-262/32, dated June 13, 1984. Work done at Hazleton Laboratories Europe Ltd, in England.

Reviewed by:

Byron T. Backus
Toxicologist
Toxicology Branch

Byron T. Backus 01-18-85

1/17/85

Approved by:

Robert Zendzian, Ph.D.
Acting Section Head
Toxicology Branch

Core Classification: Minimum (as an oncogenicity study)
Supplementary (as a 2-year feeding study)

Conclusions:

1. The study has demonstrated that the test material (or one of its metabolites) is an oncogen. Bladder carcinomas were observed at termination in 8/49 male and 5/48 female rats at the highest exposure level (5000 ppm). More than half (25/49 males, 28/48 females) the rats at this exposure level had papillomas of the bladder, and almost all had epithelial hyperplasia of the bladder. Epithelial hyperplasia of the bladder was also present in 10/50 males and 5/49 females at the 1000 ppm exposure level, and one male in this group with hyperplasia also had a bladder papilloma.

2. Although not statistically significant, the increased incidence of uterine carcinoma in 5000 ppm group females as compared to controls (8/48 vs. 3/49) may also be an exposure-related oncogenic effect.

3. A NOEL for the feeding study was not established for males; as mean body weights for males of the 200 ppm group were lower than those of controls throughout the study (and were significantly lower during the period from 2 to 20 weeks). This effect was part of an exposure-related trend. A NOEL

was established for females at 200 ppm.

4. In both males and females at 1000 ppm there was a slight increase in incidence and degree of neuropathy of the sciatic nerve at the end of the study above that seen in controls. There was 1-5% reduction (often significant at $p \leq 0.05$) in mean body weight relative to that of controls during the study, and there was a greater incidence of epithelial hyperplasia of the bladder.

5. At 5000 ppm there were significant (generally at $p \leq 0.01$) depressions in body weights for both males and females, along with significantly less food consumption throughout the study. At termination, there were increases in incidence and severity of neuropathy and muscular atrophy. Mean plasma ChE activities of females were lower (significant at 13, 26 and 52 weeks) than those of controls. Females had significantly higher concentrations of blood urea at 6, 12 and 18 months. Other effects (increased incidence of splenic atrophy, 4/10 males showing increased thromboplastin times at 24 months) probably indicate that this group was somewhat less healthier than controls and rats at 200 and 1000 ppm.

Materials:

SPF rats, strain BOR:WISW (SPF Cpb) from Winkelmann, Borchen.

Test material, designated as BOQ 5812315 (a mixed batch from batches numbered 234001222-234001226), with 99.4% active ingredient.

Procedure:

Sixty rats of each sex were randomly assigned to each of four groups, which received 0, 200, 1000 or 5000 ppm of the test material mixed in with the diet for the next 106 weeks. Rats were caged singly.

During the study diet mixtures were analyzed. According to a report at the end (pages 845-846) of the study mixtures containing 200, 1000 and 5000 ppm of the test compound were analyzed every 3 months using HPLC. There was also a test for homogeneity of the test compound in the 200 and 5000 ppm diets on one occasion, and a single 10-day storage stability test.

Rats were inspected twice daily (once on weekends and holidays). Changes or signs were recorded on a weekly basis. Rats were weighed weekly (except from week 27 to 61 when this was done biweekly). Weekly food consumption was determined by weighing the uneaten food.

Clinical laboratory examinations were carried out on blood and urine from 10 males and 10 females of each dose group at 6, 12, 18 and 24 months. Insofar as was possible the same animals were used on each of these dates. Measurements were made on the following hematology parameters:

Erythrocyte count	MCV value	MCHC
Leucocyte count	Haemoglobin	Haematocrit
Thrombocyte count	MCH	Differential count (Wright's method)

Thromboplastin time was determined at the end of the study.

The following clinical chemistry measurements were made:

Alkaline Phosphatase (ALP)	Glutamate Pyruvate Transaminase (GPT)
Glutamate Oxalacetate Transaminase (GOT)	Cholinesterases (RBC and Plasma)*

*Cholinesterase measurements were also made at 13 weeks.

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The amounts of the following were measured in the plasma:

Creatinine	Blood sugar	Bilirubin
Urea	Cholesterol	Total protein

Serum concentrations of Na, K and Ca were determined.

The urine was examined for glucose, blood, protein, pH, ketone bodies, bilirubin, urobilinogen and protein. The sediment was examined microscopically after centrifugation.

Rats which died or were sacrificed in a moribund condition during the study study were dissected and grossly appraised. Organs and tissues which appeared still evaluable were fixed in 10% formaldehyde.

At 52 weeks 10 males and 10 females randomly selected from each group were anesthetized with diethylether and sacrificed by exsanguination. They were then dissected and grossly examined. At 106 weeks all survivors were similarly sacrificed.

The following organs and tissues were fixed in 10% formaldehyde solution:

Aorta	Stomach
Eyes	*Spleen
Intestine (duodenum, jejunum, ileum colon, "partly" caecum and rectum)	*Adrenals
Femur en bloc with skeletal musculature and n. ischiadicus	*Kidneys
Brain	*Ovaries
Urinary bladder	Pancreas
*Heart	Prostate
*Testicles	Spinal marrow
Pituitary	Seminal vesicle
Salivary glands	Sternum
*Liver	Thyroids
*Lung	Esophagus and trachea en bloc
Lymph nodes (mesenteric and "non-mesenteric")	Thymus (when present)
	Uterus
	All grossly apparent "alterations"

Organs marked with an asterisk were weighed.

Tissue specimens from all rats were processed to paraffin blocks, sectioned at a nominal 5 um and stained with hematoxylin and eosin. Because bladder effects were suspected additional slides were prepared from this organ when there was sufficient additional fixed tissue available.

Statistics:

Arithmetic group means, standard deviations, and upper and lower confidence limits for 1 - alpha = 95% and 1 - alpha = 99% were calculated.

Results:

Analysis of the diet for test material indicated concentrations ranging from 82 to 129% of the theoretical value (p. 845). Homogeneity was apparently tested on only a single occasion (but it is not stated when). Results (p. 846) indicate on this one occasion the 200 and 5000 ppm diets were homogeneous, but it is not certain how samples were selected other than "by means of random numbers." Another series of analysis (p. 846) indicate the compound was "stable in the diet for 10 days" at levels of 200 and 5000 ppm.

There were no exposure-related differences in mortality between groups. No signs of cholinesterase inhibition were observed.

Mean body weights for females at 200 ppm were essentially the same as those of controls. Mean body weights for males at 200 ppm were depressed relative to controls thoughout the study, but this was statistically significant only from week 2 through 20, and again briefly at week 33 through 35. Mean body weights for both males and females at 1000 ppm were generally lower than control values, and differences were frequently significant at $p \leq 0.05$. For rats at 5000 ppm mean body weights were significantly ($p \leq 0.01$) lower than control values during the entire study.

Mean food consumption, expressed on a grams/week/body weight basis, was obviously depressed in both male and female rats at 5000 ppm throughout the study (the table running from page 134 through 142 does not give a statistical analysis). Mean food consumption for rats at 1000 ppm usually (but not invariably) was less than the corresponding control value. Females at 200 ppm showed no difference from controls, but mean food consumption for males at 200 ppm was generally less than control values; however, this was not dose-related as on more than 50 occasions mean food consumption for males at 200 ppm was less than that for males at 1000 ppm.

Hematology:

Mean HGB values for 5000 ppm females were significantly greater ($p < 0.01$) than corresponding control values at 6, 12 and 18 months; for males at 5000 ppm this occurred only at 6 months. Males at 5000 ppm showed a slight elevation in HGB relative to controls at 18 months, but this was not statistically significant at $p \leq 0.05$.

Mean thromboplastin time (measured only at 24 months) was greater in males at 5000 ppm than in controls (as calculated from individual data on pages 335-336); although probably significant the data were not analyzed statistically. Four of 10 males at 5000 ppm had thromboplastin times greater than 17 seconds, greater

than any male from any of the groups. Among females, one rat at 1000 and one at 5000 ppm (data on pages 339-340) were the only subjects showing thromboplastin times greater than 17 seconds, but differences between the means of the different groups were probably not statistically significant.

In the blood differential counts, males at 5000 ppm consistently showed a slightly higher (but not significantly different) mean eosinophile count relative to controls and the other 2 groups. In females at 5000 ppm the mean eosinophile count was significantly greater than that for controls at 6 months ($p < 0.05$) and at 24 months ($p < 0.01$). However, there are no exceptionally high values in the individual data (p. 313-338) for any of the rats at 5000 ppm.

Variations in the other haematology measurements were incidental, with no consistent trend or evidence for an exposure-related pattern apparent.

Clinical chemistry:

There was a tendency for high-exposure rats to show less mean glutamic oxalacetic transaminase (GOT) activity than controls. The following is from the tables on pages 20-23:

Males	6 months	12 months	18 months	24 months
200 ppm	0	0	0	-
1000 ppm	---	0	0	---
5000 ppm	---	---	--	---
Females				
200 ppm	-	+	+	0
1000 ppm	--	+	-	0
5000 ppm	---	0	--	-

\+ higher than controls, but no statistically significant difference
0 essentially the same activity as controls
\- lower activity than controls, but no statistically significant differance
-- lower activity than controls, $p < 0.05$
--- lower activity than controls, $p \leq 0.01$

Females at 1000 ppm had higher ($p < 0.01$) mean urea concentrations at 6 months. Females at 5000 ppm had significantly higher mean urea concentrations at 6, 12 and 18 months. However, at 24 months mean urea concentrations were essentially the same for controls and 5000 ppm female rats (Tables 7b, 8b, 9b and 10b, pages 21-24).

Males at 5000 ppm had higher mean cholesterol levels at 6 and 12 months ($p \leq 0.01$) and again at 18 months ($p < 0.05$). Mean cholesterol levels were about the same for controls and 5000 ppm male rats at 24 months.

Mean plasma ChE activities of 5000 ppm females were consistently lower (significant at $p < 0.05$ at weeks 13, 26 and 78) than control values. From the data in table 11, p. 25, the mean plasma ChE activities (with controls = 1.000 for the different female groups were:

	week 13	week 26	week 52	week 78	week 104
200 ppm	1.377	1.275	1.345	1.369	1.364
1000 ppm	0.968	1.010	0.995	1.150	1.170
5000 ppm	0.805	0.785	0.850	0.856	0.949

The consistency of these values for each group is striking.

Mean RBC ChE activities for males at 5000 ppm were significantly ($p \leq 0.01$) less than those of controls at weeks 26 and 104; females at 5000 ppm had significantly ($p \leq 0.01$) less mean RBC ChE activity than controls at 13 weeks. However, no consistent trends were evident on other occasions.

Although the report states (p. 27) that there was a dose-related statistically significant variation in Na ion in males at 18 months, this situation (with a trend of increasing Na ion concentration with exposure level) was observed only on this one occasion. Females at 5000 ppm showed significant reductions in Ca at 18 and 24 months.

Histopathology:

Mean organ weights of the 5000 ppm rats tended to be significantly less than those of controls. However, rats at 5000 ppm had mean body weights which were significantly less than those of controls throughout the study. Mean organ to body weight ratios from 5000 ppm rats were usually significantly (often at $p \leq 0.01$) greater than those of controls.

Although not statistically significant, there was a greater incidence of splenic atrophy in rats at 5000 ppm than in controls and animals at 200 and 1000 ppm; from table 3, p. 533:

	0 ppm		200 ppm		1000 ppm		5000 ppm	
	M	F	M	F	M	F	M	F
Splenic atrophy	3/49	3/49	2/50	1/46	1/50	2/49	7/49	5/48

Splenic atrophy was a finding in 7/13 males and 4/12 females of the high dose group which died "sporadically" and were examined. Corresponding values for the controls were 3/12 males and 2/11 females.

In rats at 5000 ppm there was a definite increase in incidence and degree of both neuropathy of the sciatic nerve and muscular atrophy. Although not statistically significant, the slightly greater incidence of neuropathy in 1000 ppm rats appears to be part of a dose-related trend. From table 22, p. 33 (also table 8, p. 547) for rats which were terminated at the end of the study:

	0 ppm		200 ppm		1000 ppm		5000 ppm	
neuropathy, n. ischiadicus	M	F	M	F	M	F	M	F
not examined:	0	0	0	1	3	2	0	1
not observed:	13	13	14	13	12	11	1	5
very slight:	14	17	21	14	17	12	9	3
slight:	8	7	9	11	6	13	13	17
medium:	2	1	0	1	3	2	10	9
severe:	0	0	0	0	0	0	3	1

muscular atrophy	0 ppm M	0 ppm F	200 ppm M	200 ppm F	1000 ppm M	1000 ppm F	5000 ppm M	5000 ppm F
not observed:	34	37	43	40	39	40	17	26
very slight:	3	0	1	0	0	0	8	6
slight:	0	1	0	0	0	0	7	4
medium:	0	0	0	0	2	0	3	0
severe:	0	0	0	0	0	0	1	0
number animals examined	37	38	44	40	41	40	36	36

The values above differ slightly from those in table 3, p. 532:

	0 ppm M	0 ppm F	200 ppm M	200 ppm F	1000 ppm M	1000 ppm F	5000 ppm M	5000 ppm F
Sciatic n. neuropathy p. 33 cumulative total any observed	24	25	30	26	26	27	35	30
Sciatic n. neuropathy p. 532	25	25	32	27	30	27	38	34

The differences are due to findings in some of the rats which died before final sacrifice at 106 weeks.

By assigning values to the degree of sciatic neuropathy (0 = not observed, 1 = very slight, 2 = slight, 3 = medium, and 4 = severe) and using the data in table 22, p. 33 a quantitative mean for each group can be obtained:

Males

		0 ppm	200 ppm	1000 ppm	5000 ppm
not observed	0	0 = 13 x 0	0 = 14 x 0	0 = 12 x 0	0 = 1 x 0
very slight	1	14 = 14 x 1	21 = 21 x 1	17 = 17 x 1	9 = 9 x 1
slight	2	16 = 8 x 2	18 = 9 x 2	12 = 6 x 2	26 = 13 x 2
medium	3	6 = 2 x 3	0 = 0 x 3	9 = 3 x 3	30 = 10 x 3
severe	4	0 = 0 x 4	0 = 0 x 4	0 = 0 x 4	12 = 3 x 4
Group Mean		36/37 = 0.97	39/44 = 0.89	38/38 = 1.00	77/36 = 2.14

Females

		0 ppm	200 ppm	1000 ppm	5000 ppm
not observed	0	0 = 13 x 0	0 = 13 x 0	0 = 11 x 0	0 = 5 x 0
very slight	1	17 = 17 x 1	14 = 14 x 1	12 = 12 x 1	3 = 3 x 1
slight	2	14 = 7 x 2	22 = 11 x 2	26 = 13 x 2	34 = 17 x 2
medium	3	3 = 1 x 3	3 = 1 x 3	6 = 2 x 3	27 = 9 x 3
severe	4	0 = 0 x 4	0 = 0 x 4	0 = 0 x 4	4 = 1 x 4
Group Mean		34/38 = 0.89	39/39 = 1.00	44/38 = 1.16	68/35 = 1.94

Six males (409, 412, 413, 417, 419 and 420) in the 5000 ppm group had atrophied musculature in the rear extremities (refer to the table of gross pathological findings, p. 503-505). The only other rat in the study reported in gross pathological findings as having atrophied musculature was #86, a control female. In the individual animal pathology reports (p. 770-776) the muscle findings for these rats are:

409. Atrophy: minimal multifocal.
412. Atrophy: slight multifocal.
413. Atrophy: minimal focal
417. Lesion: atrophy described at necropsy not apparent histologically
419. Atrophy: moderate multifocal
420. Atrophy: slight multifocal

It is noteworthy that these 6 cases occurred in a relatively short subject numerical sequence.

Bladder effects:

At the interim (one year) sacrifice 4/10 males and 2/10 females at 1000 ppm and all 10 males and 10 females at 5000 ppm had urethelial hyperplasia of the bladder. One male at 5000 ppm had a papilloma of the bladder.

For animals dying during the study or sacrificed at termination incidences of urothelial hyperplasia of the bladder were (from table 3, p. 529):

	controls	200 ppm	1000 ppm	5000 ppm
Males	1/49	1/50	10/50	44/49
Females	0/49	0/46	5/49	48/48

The degree and extent of urothelial hyperplasia of the bladder were also correlated with exposure level. Males at 0 and 200 ppm (rats #24 and #158 respectively) had "minimal focal" hyperplasia. In some rats at 1000 ppm the finding is reported as "diffuse" or "multifocal," while rats at 5000 ppm tended to have a diffuse hyperplasia which was either "moderate" or "marked."

Almost all papillomas of the bladder occurred in males and females at 5000 ppm with one 1000 ppm male also with this finding; all rats with bladder papillomas also had urothelial hyperplasia. From table 4, p. 535:

	controls	200 ppm	1000 ppm	5000 ppm
Males	0/49	0/50	1/50	25/49
Females	0/49	0/46	0/49	28/48

Carcinoma of the bladder occurred only in male and female rats of the 5000 ppm exposure group; from table 4, p. 535:

	controls	200 ppm	1000 ppm	5000 ppm
Males	0/49	0/50	0/50	8/49
Females	0/49	0/46	0/49	5/48

Associations of urothelial hyperplasia, papillomas and carcinomas of the bladders are given in table 26b (p. 40):

	0 ppm		200 ppm		1000 ppm		5000 ppm	
	M	F	M	F	M	F	M	F
epithelium alone	1	0	1	0	9	5	13	15
epithelium + papilloma	0	0	0	0	1	0	25	28
hyperplasia of bladder epithelium + carcinoma	0	0	0	0	0	0	6	5
papilloma + carcinoma	0	0	0	0	0	0	0	0
bladder carcinoma alone	0		0	0	0	0	2	0

In two cases (animals 362, 369) among males at 5000 ppm bladder carcinoma, but no hyperplasia of the bladder epithelium, was reported. However, in both rats the carcinoma was probably of urothelial origin (animal 362: the carcinoma is described as "a large urothelial proliferation extending into the lumen of the bladder..." In animal 369 the carcinoma was "a large exophytic proliferation of plump urothelial cells focally invading the base of the stalk").

The individual animal pathology data descriptions of the bladder carcinomas indicate that most (at least 11 out of 13) were probably derived from urothelial tissue.

Uterine carcinoma:

The incidence of carcinoma of the uterus is given below (from table 7, p. 545):

	0 ppm	200 ppm	1000 ppm	5000 ppm
Non-metastatic:	2	2	1	3
Metastatic:	1	2	2	5
Total carcinomas:	3	4	3	8

There was a increased incidence of uterine carcinoma in females at the highest exposure level, although this increase was apparently not statistically significant. Nevertheless, there was an exposure-related trend, and there was a definite tendency for these carcinomas to develop earlier and/or to grow more rapidly in females at the highest-dose level than in the other groups.

Discussion:

The study demonstrates oncogenic effects occurring in an exposure-related pattern with the test material. Oncogenic effects were papillomas and carcinomas of the bladder in both males and females. The increased incidence (although not statistically significant it was more than twice that observed in controls) of uterine carcinoma in 5000 ppm females also may have been an oncogenic effect. There may be a similarity in the uterine and bladder environments that makes these organs more susceptible than others to the development of carcinomas on exposure to the test material or one of its metabolites.

On p. 41 a statement is made that: "...the increased incidence of hyperplasia of the bladder, noted at the interim autopsy after one year from the dose of 1000 ppm onwards, was not observed at end of study, but this condition occurred...in the 5000 ppm dose group." However, a number of rats in the 1000 ppm group showed exposure-related urothelial hyperplasia at the end of the study. The registrant then appears to attempt an argument that the bladder carcinomas were not necessarily related to the papillomas and/or epithelial hyperplasia of the bladder, as no joint occurrences were found of papillomas and carcinomas, and there were two carcinomas of the bladder in the 5000 ppm group

in which no epithelial hyperplasia of the bladder was found. This section was apparently written at Wuppertal-Elberfeld, rather than at Hazleton Laboratories of Europe, where the actual histologic observations were made.

Although the report states that there were no associations of papillomas with carcinomas, individual animal pathology data suggest this is somewhat equivocal. In animal 375 the carcinoma was "a large partly papillary partly solid exophytic proliferation of urothelial cells..." In animal 412 (not considered to have bladder carcinoma) a papilloma was a "small endophytic proliferation of nests of small cells extending into submucosa. Equivocally early carcinoma." In animal 457 the carcinoma was "a large exophytic papillary growth."

With respect to the occurrence of bladder carcinomas without urothelial hyperplasia, it is noted on p. 44: "In the case of the two bladder carcinomas in the 5000 ppm group males, where no hyperplasia of the bladder epithelium was recorded, it cannot be ruled out that locally hyperplastic areas existed in in the bladder epithelium which were, however, not contained in the histological plane of section, and which therefore were not recorded."

Among non-oncogenic effects, all groups of treated males showed depressed body weights with respect to controls, and the degree of depression was correlated with the degree of exposure to the test material. A NOEL was not observed with respect to body weight depression, although this effect was statistically significant for the 200 ppm males only during the period from weeks 2 through 20 (and again briefly during weeks 33-35). Among females, only the rats at 1000 and 5000 ppm showed depressed body weights with respect to control values.

The most serious non-oncogenic effects included a neuropathy and probably associated muscular atrophy, both definitely present at 5000 ppm. A slight (not statistically significant) increase in severity of neuropathy appears to be present at 1000 ppm, and it is possible that the "medium" muscular atrophy observed in two males at 1000 ppm was also due to exposure to the test material.

The greater incidence of splenic atrophy at 5000 ppm, even though not statistically significant, may be an effect. The initial interpretation was that its occurrence was simply an indication that the high-dose rats were in somewhat poorer health than rats in the other groups, but the report (submitted along with this study) that two of the metabolites of Baygon have a suppressive effect on programmed DNA synthesis in rat spleen cells suggersts a possibly more direct cause and effect relationship.

The situation with respect to most of the haematology and clinical chemistry values also probably indicates that the animals at 5000 ppm tended to be in poorer health than those of other groups. This would explain the greater mean thromboplastin time for males at 5000 ppm at 24 months, and the tendency for both males and females in this group to have less mean glutamic oxalacetic transaminase (GOT) activity.

However, the plasma ChE depression in 5000 ppm females may have been a direct effect of exposure to the test material.

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

005896

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): Thyssen, 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" 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. 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.

005396

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 T. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) 12.17.84

005896

DATA EVALUATION REPORT VII

STUDY TYPE: Primary eye 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): 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.

005896

005896

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.

83-2 (MOUSE)

005896

DATA EVALUATION REPORT COVER
FOR ~~BBCR07~~ MRID 100546

005896

Reviewed by: R. P. Zendzian 06/21/82 (Coberly file #002156)

Secondary reviewer: William Butler Acc. 070831

Reviewed by: B. T. Backus 03/04/87

Secondary reviewer: M. van Gemert

CONCLUSIONS:

In the initial review by R. Zendzian concern was expressed about the highest dose level (6000 ppm, equal to 1191 mg/kg/day in male and 1374 mg/kg/day in female mice) in terms of acute oral toxicity.

Subsequently, material was submitted and reviewed (B. Backus, 03/04/87) and was accepted as providing an adequate enough explanation as to the ability of mice to survive a 6000 ppm dose level of Propoxur in their diet.

The mouse oncogenic study is therefore classified as minimum.

Byron T. Backus 05/01/87

Byron T. Backus, Toxicologist
Review Section III
Toxicology Branch, HED

83-2 (Mouse)
MRID 100546

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C 20460

002156

005896

MEMORANDUM

TO: J. S. Ellenberger, PM-12
Registration Division (TS-767)

FROM: Robert. P. Zendzian, Ph.D.
Toxicology Branch/HED (TS-769)

6/21/85

THRU: William Burnam, Head
Review Section III

and

William Burnam, Deputy Chief
Toxicology Branch, HED

SUBJECT: Baygon(R) PP# 2F1244, Review of Two-year Mouse Oncongenicity Study and Teratogenicity Study, Caswell #508

Attached are my reviews of Bayer Report No. 9954 and Bayer Report # 10183 submitted by Mobay Chemical Corporation in relation to PP# 2F1244. The results of my reviews are summarized as follows:

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

The study shows no evidence of oncogenicity in mice at doses up to 6000 ppm (1191 mg/kg/day males and 1374 mg/kg/day females). The study satisfies the requirements for mouse oncogenicity; however, there is a discrepancy between the doses used and the acute oral toxicity of the compound.

In this study the calculated high-dose animals consumed 1191 mg/kg/day for males and 1374 mg/kg/day for females. The compound is a carbamate cholinesterase inhibitor and its reported LD_{50} in rats is on the order of 100 mg/kg orally. Feeding studies with carbamate cholinesterase inhibitors often show an apparently lesser toxicity than the acute oral studies but the difference here appears excessive. Several possible explanations exist for this difference.

1. The mouse may be considerably less sensitive to Baygon than the rats and the large difference is illusionary.

2. The compound deteriorates when mixed with food.

3. The compound bonds to the feed.

4. Preparation of the dosed feed was in error, and the true dose was lower than calculated.

In order to clarify this matter the following information is requested from the registrant:

1. An acute oral LD_{50} in males and females of the strain of mice used for the oncogenicity study.

2. A stability test of Baygon in the mouse diet at the doses used in the studies.

3. Photo or xerographic copies of the laboratory records of dose preparation for this study.

4. If the first three requirements do not clarify the toxicity discrepancy, a metabolism study utilizing radio-labeled Baygon in feed may be necessary.

BOE 5812315 [Propoxur, the Active Ingredient in Baygon(R)] Study of Embryotoxic and Teratogenic Effects on Rabbits After Oral Administration. G. Schlueter, Bayer A.G.; Institut Fuer Toxikologic; Bayer Report # 10183; Mobay ACD Report # 80034, September 9, 1981.

Teratogenic and/or fetotoxic effects were not demonstrated in rabbits at doses of Baygon(R) up to 10 mg/kg/day (days 6 through 18 of pregnancy). No toxic and/or pharmacologic effects occurred in the dams at any dose. Proper performance of this type of study requires that the high dose produce some effect in the dam (or be as high as can be practically administered). The study should be repeated at higher doses.

In relation to this petition, Toxicology Branch wishes to remind you of the data requested by Dr. Dykstra in his memo of June 26, 1981.

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"Recommendation:

The chronic rat and dog studies with Baygon submitted with PP# 9G0765 and 2F1244 did not adequately characterize the NOEL for cholinesterase inhibition (for plasma, RBC, and brain). Therefore, two 90-day feeding studies (rat and dog) with technical Baygon designed to measure these cholinesterase activities and to demonstrate a NOEL are required to be submitted."

Data Evaluation Report

002156

005896

Two-Year Mouse Oncogenicity Study

Compound Propoxur, Baygon(R), BOE 5812315, Technical

Citation

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

Reviewed by
6/8/82
Robert P. Zenczian, Ph.D.
Pharmacologist
Toxicology, Branch HED

Core Classification Minimum, (may be upgraded).

Conclusion: The study shows no evidence of oncogenicity in mice at doses up 6000 ppm (1191 mg/kg/day males and 1374 mg/kg/day females). The study satisfies the requirements for mouse oncogenicity; however, there is a discrepancy between the doses used and the acute oral toxicity of the compound.

The doses ingested are 11 and 13 times the acute oral toxicity of Baygon(R) in rats. Since the explanation of this difference in toxicity can range from a much lower sensitivity in mice to an error in dose preparation it is necessary to secure additional information before accepting the study. The information required is presented in detail in the discussion part of this report.

Materials

1. Test Compound

Technical BOE 5812315, (Propoxur, Baygon(R), batch #75/40, purity 99.6%) was used for the first 6 weeks of the study. Starting with week 7 a 90% concentration of Propoxur in [redacted] was used. "The stability of the compound in the mouse feed over the time period involved was assured by analytical tests

performed before the start of the study." Results of these tests were not provided.

2. Experimental Animals

SPF mice (CF_1/W74, bred by Winkelmonn, Borchan, FRG) were used for the study. Mice were 5-6 weeks old at the start of the study. The mean weight of the males was 25 gm and of the females 22 gm. The animals were housed in Type I Mikrolen cages on wood shavings, room temperature 22 ± 2 o C and on a 12 hour light/dark cycle. Cages were cleaned and supplied with fresh food weekly. Water was available ad libitum. The number of animals housed per cage was not reported.

Methods

1) Duration

Approximately 24 months (June 1976 to July 1978).

2) Dosing

BOE 5812315 was mixed with pulverized feed to produce concentrations of 0 (control), 700, 2000 and 6000 ppm. Sixty males and 60 females were used at each dose. Ten of each sex per dose level were used for laboratory examination and interim necropsy. The body weights and food consumption of these latter animals were not determined.

3) General Observations.

All animals were observed daily for visable abnormalities. Body weight was determined weekly for the first 13 weeks and at 2-week intervals thereafter. Weekly food consumption was determined by "sex within each test group."

4) Clinical Chemistry and Hematology

Blood analysis was performed on 5 males and 5 females from each test group at 6 and 12 months on study and on 10 males and 10 females from each group at termination of the study.

Hemotological determinations
- Erythrocyte count
- Leukocyte count
- Thrombocyte count
- Reticulocyte count
- Differential WBC count
- Hemoglobin
- Hematocrit

Clinical Chemistry
- Alkaline Phosphatase
- Glutamate oxaloacetate transaminase
- Glutamate pyravate transaminase
- Creatinine
- Urea
- Blood Glucose
- Cholesterol
- Bilirubin
- Total Protein

5) Gross Necropsy and Histopathology

Gross necropsy was performed on all animals that died during the study, on 5 males and 5 females from each test group sacrificed at 6 months and on all remaining animals which were sacrificed at the end of the study. Samples of heart, lungs, liver, spleen, kidneys, testes, brain, pituitary, thyroid, adrenals, stomach, pancreas, urinary bladder, ovaries and uterus, epididymides, seminal vesicle, prostate, trachea, esophagus, femur with skeletal musculature and all abnormal tissue found during necropsy were collected and preserved for histopathological examination. The heart, lungs, liver, spleen, kidneys and testes were weighed.

Slide preparation and histopathological examination were performed by Hazleton Laboratories, Europe Ltd., Harrogate, England.

6) Statistical Analysis

Means, standard deviations and upper and lower confidence limits at 95% and 99% were calculated for each experimental group on all numerical data.

The U test of Mann, Whitney and Wilcoxon was used to compare control with test values at the 5% and 1% levels of significance.

Mortality rates of test and control groups were compared by means of Fishers exact test at significance levels of 5% and 1%.

Results

1) Observations

No differences in appearance and general behavior between test and control groups were reported.

2) Food and compound consumption

No differences in food consumption between control and treated animals was observed. The actual dose per animal was calculated as:

ppm	700	2000	6000
Males			
mg/kg/day	139	367	1191
Females			
mg/kg/day	192	478	1374

3) Body weights

Females at all doses and males at 700 and 2000 ppm gained weight in a similar manner as the controls. Males at 6000 ppm were significantly lower in body weight than controls for most of the study.

4) Mortality

The data present some evidence of decreased mortality at 2000 and 6000 ppm for the duration of the study. Percent mortality with time is summarized below.

Week	6	12	18	24
Sex	m/f	m/f	m/f	m/f
Dose ppm				
0	4/2	14/10	42/34	80/84
700	4/6	20/26	60/44	74/78
2000	2/2	10/14	38/36	68/68
6000	2/6	10/8	28/22	66/64

5) Hematology

No compound related abnormalities were observed in the cellular components of the blood. A few statistically significant variations from control were reported but they were inconsistent, following no apparent pattern in dose and/or time.

6) Clinical Chemistry

No dose and/or time related abnormalities were reported. Scattered values differed significantly from control but they followed no pattern.

7) Gross Pathology

No compound related effects were reported in the animals that died on study and in the animals that were sacrificed at 6 months and at termination.

8) Mean organ weights

Scattered mean values for the test animals at termination differed significantly from controls. Only the values for testes could be considered compound related but this is not considered a direct toxic effect. Control termination mean weight (181 mg) differed significantly from control 6 month mean weight (256mg). This is indicative of the normal decrease in testes weight in aged male mice. Treated testes mean weights were higher (215, 208 and 210 mg) at termination. This can be directly related to the compound induced increase in survival of the treated animals.

9) Histopathology

Nonneoplastic changes

No compound related changes were observed in any organs or tissues of the treated mice.

Neoplastic changes

The major tumor types observed were Adenoma and Adenocarcinoma of the lungs in both sexes, Adenoma and Adenocarcinoma of the liver in the males and malignant lymphoma in both sexes.

The incidence of these tumor types did not exceed that of historical controls and there was no evidence of a dose related increase. Occurrence of other tumor types was scattered with no dose relationship.

Discussion

The study follows the requirements for a mouse oncogenic study. The only compound related effects observed were a decrease in weight gain in the high dose males and an increase in survival time in both sexes. No oncogenic effect was observed. In and of itself the study satisfies all requirements for a mouse oncogenic study however there are some discrepancies between the doses used in this study and previous studies that require clarification.

In this study the calculated high-dose animals consumed 1191 mg/kg/day for males and 1374 mg/kg/day for females. The compound is a carbamate cholinesterase inhibitor and its reported LD_{50} in rats is in the order of 100 mg/kg orally. Feeding studies with carbamate cholinesterase inhibitors often show an apparently lesser toxicity than the acute oral studies but the difference here appears excessive. Several possible explanations exist for this difference and it is necessary to have this clarified.

1. The mouse may be considerably less sensitive to Baygon than the rat and the large difference is illusionary.

2. The compound deteriorates when mixed with food.

3. The compound bonds to the feed.

4. Preparation of the dosed feed was in error and the true dose was lower than calculated.

In order to clarify this matter the following information is requested from the registrant:

1. An acute oral LD_{50} in males and females of the strain of mice used for the oncogenicity study

2. A stability test of Baygon in the mouse diet at the doses used in the studies

3. Photo or xerographic copies of the laboratory records of dose preparation for this study

4. If the first three requirements do not clarify the toxicity discrepancy a metabolism study utilizing radio labeled Baygon in feed may be necessary.

CAPITAL FILE

005896

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

MAR 4 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: BAYGON - Company response

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, Review Section III
Toxicology Branch (TS-769C)

and

Theodore M. Farber, Ph.D.
Branch Chief
Toxicology Branch (TS-769C)

EPA ID. No. 9H5199

Project No. 1844

Tox. Chem. 508

Action Requested:

The Registrant has submitted a response to previous Toxicology Branch reviews (R. Zendzian, Dec. 23, 1985; Aug. 16, 1982) regarding the highest dose level (6000 ppm) in a 2-year mouse oncogenicity study.

Background:

In the previous toxicology reviews concern was expressed about a possible discrepancy between the 6000 ppm Baygon that mice received in their diet over a 2-year period (calculated in these reviews as equivalent to 1191 mg/kg/day for males and 1374 mg/kg/day for females: using the usual conversion factor of 1 ppm = 0.015 mg/kg/day for mice 6000 ppm would be 900 mg/kg/day) and an acute oral LD50 value for the technical of approximately 100 mg/kg.

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Comments and Recommendations:

1. The submitted literature indicates that mice can withstand a dosage level of 6000 ppm Propoxur when it is administered in their diet. As the registrant also notes, because mice tend to feed at night there is a possibility that cholinergic symptoms may have occurred which were not noted because there was rapid recovery and observations were made only during the day.

2. The report entitled "Tolerance to the Carbamate Insecticide Propoxur" (Costa, L. G., Hand, H., Schwab, B. W. and Murphy, S.D. Toxicology 21: 267-278, 1981), indicates that mice can also develop an ability to metabolize (and detoxify) Propoxur as a result of exposure to this material over a period a few weeks.

3. The registrant has adequately addressed the previous question raised by the Toxicology Branch as to the ability of mice to survive 6000 ppm Propoxur in their diet.

83-3 (RAT)
MRID 45094

Reviewed by: Byron T. Backus Byron T. Backus 07/30/87
Section 3, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D. mvanGemert 5/5/87
Section 3, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT I

STUDY TYPE: Teratology - rat TOX. CHEM. NO.: 508

ACCESSION NUMBER: 091768 MRID NO.: not given

TEST MATERIAL: Technical Propoxur, 98.4% active

SYNONYMS: BAYGON, UNDEN, BLATTANEX, BAY 39007

STUDY NUMBER(S): Pharma report No. 2388

SPONSOR: Bayer

TESTING FACILITY: Bayer AG Institute of Toxicology

TITLE OF REPORT: Bay 39007 Examinations for Embryotoxic Effects Among Rats

AUTHOR(S): Dr. D. Lorke

REPORT ISSUED: 11-16-70

Classification: core-supplementary

Special Review Criteria (40 CFR 154.7)

BACKGROUND:

This is an older report, previously reviewed (July 10, 1972). In this review the conclusion was stated:

> "Feeding...at 10000 ppm was embryotoxic based upon increased resorptions and decreased living fetuses. 3000 ppm produced less severe effects in the fetuses while 1000 ppm was tolerated without any damages. No teratogenic effects were observed from the feeding of BAY 39007 at levels up to 10000 ppm."

According to the (current) one-liner summary associated with this review the maternal (and fetotoxic) NOEL's were 1000 ppm with LEL's of 3000 ppm.

COMMENTS AND CONCLUSIONS:

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1. In the control females the mean weight gain was 97.4 grams; in the low-dose (1000 ppm) group it was 80.7 grams. Using a two-sample T test computation P = 0.0841 (with unequal variances, since the test for equality of variances gave a p of 0.0213). However, the mean weight gain for the control females was depressed by inclusion of data from one female which was probably sick and gained only 50 grams. Without the value for this one female (the next lowest gain was 87 grams) the control mean was 104.1 grams and that for the low dose animals was 80.7, and P = 0.0009 (with equal variances, since the test for equality of variances gave a p = 0.3035).

2. The mean fetal weights were depressed for 1000 ppm rats (controls: 4.09 g; 1000 ppm: 3.78 g; 3000 ppm: 3.51 g; 10000 ppm: 2.72 g). Although I have not run a statistical test on this depression, the lowest mean weight for any litter of the controls was 3.82 grams, and 8/10 litters for the 1000 ppm group means below this value.

3. The mean numbers of fetuses/litter showing "slight bone changes" were controls: 2.0; 1000 ppm: 4.0; 3000 ppm: 3.8 and 10000 ppm: 8.0. There is no definition of the meaning of "slight bone changes" in this report. At 3000 ppm 0.5 fetuses/litter were "underdeveloped;" at 10000 ppm 6.3 fetuses/litter were in this category (underdeveloped = 3.0 grams or less).

4. The number of animals used in this study (10 dams/dose level) clearly falls below that set (20) in the Section F Guidelines.

5. This reviewer concludes that maternal toxic and fetotoxic NOEL's were not observed, as these effects were occurring (although perhaps not at a statistically significantly elevated level) at the lowest dose (1000 ppm). Also, because of the inadequate number of animals used, as well as ambiguities in the reporting ("slight bone changes") the study does not adequately demonstrate that the test material is not teratogenic.

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A. MATERIALS:

1. Test compound: Propoxur 98.4% technical [with 0.82% isopropoxyphenol.]

2. Test animals: Species: rat, Strain: FB30, Age: 2.5-3.5 months, Weight: 200-250 g.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned in some unspecified fashion to the following test groups:

Test Group	Dose in diet (ppm)	female	Interim sac.
1 Cont.	0	10	no interim sac.
2 Low (LDT)	1000	10	no interim sac.
3 Mid (MDT)	3000	10	no interim sac.
4 High(HDT)	10000	10	no interim sac.

Females were paired overnight with males. Vaginal smears were used to determine whether insemination had occurred.

2. Diet:

The rats received Altromin R powdered feed (presumably with the test material mixed in) and tap water ad libitum during their entire gestation period. There are no dietary analyses in this report.

3. Fetal examination:

Fetuses were delivered by Caesarean under ether narcosis on the 20th day of gestation. There was "Extensive inspection of the fetus for superficial deformations, determination of the weight, killing with ether fumes, exenteriating with careful examination of the chest and abdominal organs, fixing in ethanol, clearing of the fetus and staining of the bone system with Alizarin red S, evaluation of the bone system."

4. Statistics - "The quality sum test according to WILCOXON was used for the statistic significance test (Biometrics 3, 119 (1947). A difference was regarded as significant if the probability of error was smaller than 5% ($p < 0.05$)."

5. There is no quality assurance statement.

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C. METHODS AND RESULTS:

1. Observations

"The rats that were treated with 1000 ppm did not differ from the untreated rats. The animals were lively, ate well, had smooth and clean fur and appeared healthy."

"The rats that received 3000 ppm, and even more so the ones receiving 10000 ppm in the feed, ate less. The animals were not quite as lively, their coat was somewhat rough and they did not seem quite as healthy as the control rats... Rat No. 884 (control) was ill."

2. Pregnancy rates

"From among the inseminated animals the following were pregnant:"

Dosage (ppm)	# Inseminated	Fertilized	% Fertilized
0	10	9	90
1000	10	10	100
3000	9	8	88.9
10000	10	6	60

3. Maternal body weights

The following are the mean maternal weight gains as reported for the individual groups:

Dosage (ppm)	Average	Smallest	Biggest
0	97.4	50	119
1000	80.7	70	100
3000	58.4*	22	88
10000	44.0*	5	85

*Significantly different from control at $p < 0.05$

The "smallest" weight gain for controls was 50 grams, and might have been (there is some problem with legibility) from rat 884, which was noted as being sick. Without the value from this one rat the mean weight gain for the controls was 104.1 grams, and the "smallest" weight gain was 87 grams.

4. Food consumption of dams

Dosage (ppm)	Average consumption	Consumpt(g)/day/rat
0	444 grams	22.2
1000	416 "	20.8
3000	316 "	15.8
10000	288 "	14.4

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5. Fetal examination

Dosage (ppm)	Mean no. of implant.	Mean no. of resorpt.	Mean no.of fetuses	Mean fetal wt (g)	Mean no. per litter with "slight bone changes."
0	11.9	0.9	11.0	4.09	1.9
1000	12.0	0.6	11.4	3.79	4.0
3000	12.4	2.0*	10.4	3.51	3.8
10000	10.7	5.8	4.8	2.72	8.0

*One female had 13 resorptions.

There were only 3 litters in the 10,000 ppm group in which complete resorption had not occurred.

It is reported that there were no deformed fetuses at any dose level.

D. DISCUSSION:

In the control females the mean weight gain was 97.4 grams; in the low-dose (1000 ppm) group it was 80.7 grams. Using a two-sample T test comparison P = 0.0841 (with unequal variances, since the test for equality of variances gave a p = 0.213). However, the mean weight gain for the control females was depressed by one female which might have been sick and which gained only 50 grams; without this value (the next lowest gain was 87 grams) the control mean was 104.1 grams. Using a two-sample T test and comparing with the 1000 ppm rats gave a P = 0.0009 (with equal variances, since the test for equality of variances gave a p = 0.3035).

The mean fetal weights were depressed for 1000 ppm rats (controls: 4.09 g; 1000 ppm: 3.78 g; 3000 ppm: 3.51 g; 10000 ppm: 2.72 g). Although I have not run a statistical test on this depression (no data is given for individual fetuses, only on the means per litter) the lowest mean weight for any one litter in the control group was 3.82 grams, and 8/10 litters in the 1000 ppm group were below this value.

The fetuses were not sexed.

There is no definition of the terminology "slight bone changes" within this report, although the impression this reviewer gets is that it might have related (at least to some extent) to delayed ossification. The incidence was somewhat elevated (but not necessarily significantly so) in all groups which were exposed to dietary Propoxur.

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The number of animals used in this study (10 dams/dose level) clearly falls below that set (20) in the current Section F Guidelines.

Overall, the study is clearly no better than supplementary.

While perhaps this reviewer should not have spent as much time and effort on this DER as has been done, it was felt necessary that a correction - particularly that relating to the maternal and fetotoxic NOEL's as reported in the one-liners - was in order. It is the conclusion of this reviewer that the study does not demonstrate maternal and/or fetotoxic NOEL's for Propoxur at the lowest dietary dose level given (1000 ppm), as effects (possibly statistically non-significant, but part of dose-related trends nevertheless) which included reduced maternal weight gains, reduced fetal weights, possibly delayed fetal ossification, were present even at this level.

FROM
COBERLY FILE
002156 005896
87-7 (RABBIT)
MRID 100547

Data Evaluation Report

Teratology Study in Rabbits

Compound: BOE 5812315, Propoxur, Baygon(R) Technical

Citation: BOE 5812315 (Propoxur, the Active Ingredient in Baygon(R)) Study of Embryotoxic and Teratogenic Effects on Rabbits after Oral Administration. G. Schlueter, Bayer A.G.; Institut Fuer Toxikologic; Bayer Report # 10183; Mobay ACD Report # 80034, September 9, 1981.

Reviewed by: Robert P. Zendzian, Ph.D. 6/8/82
Pharmacologist
Toxicology Branch/HED

Core Classification: Minimum

Conclusion: Teratogenic and/or fetotoxic effects were not demonstrated in rabbits at doses of Baygon(R) up to 10 mg/kg/day (days 6 through 18 of pregnancy). No toxic and/or pharmacologic effects occurred in the dams at any dose. Proper performance of this type of study requires that the high dose produce some effect in the dam (or be as high as can be practically administered). The study should be repeated at higher doses.

Materials: Technical BOE 5812315 (99.6%) received January 21, 1980 was used in this study.

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Sexually mature Himalayan rabbits, 2 to 2.5 kg, CHBB:HM strain were used for the study. The rabbits were housed singly in rabbit cages, room temperature 20 to 23°C, and 12 hours light-dark cycle. Food and water were available ad libitum.

Methods: Mating - One male and one female were caged for breeding. The day on which two copulations occurred was taken as day zero.

Dosing: The compound was suspended in 0.5% Cremophor in water solution and administered by oral intubation on day 6 through day 18 of gestation. Doses were 0 (control), 1, 3, and 10 mg/kg/day.

Observations: The animals were weighed daily and observed for abnormalities during the gestation period.

Terminal Observations: On gestation day 29, the females were sacrificed and the fetuses removed by cesarean section.

All fetuses were examined for:

1. Weight and number

2. Sex

3. External malformations

4. Gross necropsy of thoracic and abdominal organs

5. Brain malfunctions by slicing fixed sections with a razor blade

6. Cleaning and staining the skeletal system.

Statistics

1. The non-parametric rank sum test of Wilcoxen was used for weight gains, number of implantations, number of fetuses, number of resorptions, fetus weight and placenta weight.

2. The Chi-square test was used for number of fetuses with skeletal alterations, number with malformations and number stunted.

3. Either the Chi-square test or the Fisher exact test was used for the indices of fertilized and pregnant animals.

Results:

1. Effect on the dams: No toxic effects on the females were observed at any dose. No deaths occurred nor were abnormalities of appearance or behavior observed. No significant differences in weight gain between control and treated animals occurred.

There was no difference in fertilization and pregnancy indices between control and treated groups.

2. Effects on embryo and fetal development: No compound-related effects on the fetuses were observed in this study.

Discussion: The study as reported was properly performed and negative for fetal effects of doses of up to 10 mg/kg/day during gestation. However, since the highest dose produced no effects on the dam and a higher dose is technically feasible, the study does not fully satisfy the requirement for a teratogenicity study.

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BJ-T
MRID 55142

DATA EVALUATION REPORT COVER
~~FOR CBPR10~~

005896

Reviewed by: Dr. Parkin, 07/10/72

Secondary reviewer: none Acc. 091768

CONCLUSIONS:

This review is part of Coberly file #003692. The statement was made in this review that "Except for the mating period. pregnancy, littering, and the raising period for the young rats, the animals were treated with BAY 39007 during the entire testing time." Also, the statement is made in the conclusions that: "The value of this study is restricted since BAY 39007 was not fed during the mating period, pregnancy, littering, and raising period for the young rats." Note also that histopathology was conducted only on 5 F_{3b} rats/sex/group.

Examining a copy of the original submission (acc. 091768) I have determined that the statement "Except for the mating period..." was excerpted directly from this report.

My conclusion then is that this study could be classified as no better than core supplementary data, and does not satisfy the requirement for a 2-generation (rat) reproduction study.

Byron T. Backus 04/30/87

Byron T. Backus, Toxicologist
Review Section III
Toxicology Branch, HED

Nikki Gamer 5/5/87

003692

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[illegible] based upon clinical or other symptoms. No ChE NEL was determined as an unsuitable assay method was used.

J. Generation Studies on Rats (Farbenfabriken Bayer AG; 798)

1. Procedure

Groups of 10 M and 20 F FD30 breed rats were fed on diets containing 0, 250, 750, 2000, or 6000 ppm BAY 39007 Technical (purity 98.4%). Except for the mating period, pregnancy, littering, and the raising period for the young rats, the animals were treated with BAY 39007 during the entire testing time. The rats were weighed weekly and food consumption was recorded during those periods when the compound was fed.

During the mating period, 2 F rats stayed with one M for 19 or 20 days. The M rats were alternated in such a way that each F was together with 3 different M longer than the duration of a cycle. After mating the F were placed in individual cages.

Immediately after birth, the number and weight of all the young were recorded. In litters with more than 10 young, the litters were reduced to 10 by culling the weak after 5 days (the weights were redetermined). The young rats were raised to 4 weeks and weighed weekly. The young from the first mating (F_{1a}, F_{2a}, F_{3a}) were then killed.

The young from the second mating were raised to 4 weeks, separated according to sex and raised to 8 weeks when the rats to be used as the next parental generation were selected (and mated at an average age of 100 days). The remaining animals were killed.

The young rats were evaluated macroscopically immediately after birth for any deformities. The young rats from the F_{3b} generation were killed at 3 weeks of age. Two M and 2 F young from each mother were dissected and evaluated macroscopically. The thymus, heart, liver, kidneys, adrenal glands, and testes were weighed.

The following tissues from 5 F_{3b} rats/sex/group were taken for histopathological examination (H & E stain):

heart	kidneys*
gonads	liver*
spleen	adrenals
uterus	thymus

*Oil Red O stain also.

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2. Results

Significant Reproduction Changes

Parental Generation	F_0		F_{1b}		F_{2b}	
Litter	F_{1a}	F_{1b}	F_{2a}	F_{2b}	F_{3a}	F_{3b}
Fertility	-	-	-	b	-	-
Decreased litter size	b	b	b	-	a,b	b
Survival rate-4 weeks	b	a,b	b	-	b	-
Body weight-birth	a,b	a,b	b	b	b	b
Body weight-4 weeks	a,b	b	-	b	a,b	a,b

2000 ppm rats = a 6000 ppm rats = b

No compound-related changes were observed by either macroscopic or microscopic examination of the tissues at necropsy. No compound-related malformations were observed. Organ weight reductions in the 2000 or 6000 ppm groups were directly related to decreased body weights.

3. Conclusions

The value of this study is restricted since BAY 39007 was not fed during the mating period, pregnancy, littering, and raising period for the young rats. Any abnormalities or deviations which occurred in the young were a result of damage to the parental generation prior to mating, etc. In order for the effects of BAY 39007 to be directly correlated to the young rats, the compound would have to be fed during these periods.

K. Examinations of Embryotoxic Effects Among Rats (Farbenfabriken Bayer AG; 2388)

1. Procedure

Ten F FS30 rats/group were fed either 0, 1000, 3000, or 10,000 ppm 93.4% technical BAY 39007 [(+ 0.82% isopropoxphenol)] during the entire period of gestation. The young fetuses were delivered by caesarian on the 20th day of gestation. The fetuses were examined for superficial deformations, determination of the weight, chest and abdominal organ abnormalities, and skeletal deformities (stain with Alizarin red S).

BBPR01
84-2(1)(i)(A)
005896

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

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 I2,500 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.

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.

84-2(i)(j)(A)
MRID 149047

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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 84

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;

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

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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.

84-2(iv) 005896
84-3(ii)
MRID 149041

Reviewed by: Byron T. Backus
Section 3, Tox. Branch (TS-769C)
Secondary Reviewer Marcia van Gemert, Ph.D.
Section 3, Tox. Branch (TS-769C) 12.17.80

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.

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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	Number of cells with micronuclei 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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MRID 121197

DATA EVALUATION REPORT COVER
FOR ~~REPRIS~~ MRID 121197

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Reviewed by: Dr. Parkin, 08/09/72

Secondary reviewer: (probably none)

CONCLUSIONS: •

This study is acceptable insofar as identification of some of the metabolites is concerned; otherwise, it has to be considered as supplementary.

Byron T. Backus 05/04/87

Byron T. Backus, Toxicologist
Review Section III
Toxicology Branch, HED

William Stewart 5/5/87

A. Parkin 005396

007693

ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Date: August 9, 1972

Reply to Attn of:

Subject: Addendum to memorandum of July 10, 1972 for o-isopropoxyphenyl methylcarbamate (Baygon, PH# 37007) in or on various raw agricultural commodities.

To: Mr. Drew H. Baker, Jr., Chief
Petitions Control Branch
Pesticides Tolerances Division

Pesticide Petition No. 2F1244

Chemagro Corporation
P. O. Box 4913
Kansas City, Missouri 64120

TOXICOLOGICAL EVALUATION

The following studies which are pertinent to our toxicologic requirements were incorporated into Section D of the petition and were not considered in our original evaluation of toxicity data in Section C.

I. The Metabolic Fate of Baygon in the Rat (Chemagro Corp.; 28797).

A. Procedure

1. Individual rats were administered 8 mg/kg of isopropoxy-1,3-^{14}C or carbonyl-^{14}C labelled Baygon by intubation. Sodium hydroxide traps for expired gases were sampled at one hour, three hours, at 3 hour intervals thereafter through 54 hours, and at 72 hours. Toluene traps were changed at 12, 24, 48, and 72 hours. Urine and feces samples were collected every 12 hours until sacrifice at 72 hours.

2. A female rat was intubated with 10 mg/kg of labelled Baygon (isopropoxy-1,3-^{3}H and carbonyl-^{14}C in a $^{3}H/^{14}C$ ratio of 15:1). Ethanolamine traps for expired gases were sampled each hour for 9 hours and then at 12, 18, and 24 hours. The urine and feces were collected at 6, 12, and 24 hours.

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3. A rat was treated orally with 5 mg/kg of isopropoxy-1,3-[illegible]-labelled Baygon. The expired gases were collected in sodium hydroxide traps for 24 hours after treatment.

B. Results

Rats orally treated with BAYGON eliminated 85% of the administered dose within 16 hours of administration, 20-25% as volatile compounds (CO_2, acetone), and 60% in the urine as conjugates, the remainder in the feces. The major route of metabolism in rats is depropylation to 0-hydroxyphenyl N-methylcarbamate, or hydrolysis of the carbamate linkage to give isopropyl phenol. The minor metabolic pathway is believed to be ring hydroxylation at either the 5 or 6 position with secondary hydroxylation of the α-carbon of the isopropoxy group. An additional metabolic pathway can be drawn from the N-hydroxy methyl metabolite. Metabolites which are ring hydroxylated in the 2 or 6 position form N-conjugates while the others form O-conjugates.

II. The Acute Oral Toxicity of o-Hydroxyphenyl N-Methylcarbamate to Rats (18003).

Adult female rats were administered this Baygon metabolite suspended in 0.2% aqueous carboxymethylcellulose via stomach tube. Toxic doses produced tremors within one hour and death was preceded by convulsions. Death or apparent complete recovery occurred within a day of treatment. The approximate LD_{50} was 1100 mg/kg.

III. Plant Metabolism of Baygon (Chemagro Corp.; 21746).

Following foliar application of carbonyl and isopropoxy labelled Baygon C^{14} to growing plants (bean and corn) large quantities of Baygon were volatilized from the leaf surface. Baygon comprised 69-93% of the residue remaining after 5 days and 36% of the residue at 14 days. Metabolites tentatively identified were β-glucosides of o-hydroxyphenol N-methylcarbamate and o-isopropoxyphenyl N-hydroxymethylcarbamate and the corresponding unconjugated forms.

IV. Metabolism of Baygon in Corn Plants (Chemagro Corp,; 29233).

Baygon accounted for 50% of the residue at the 14-day sampling interval. β-glucosides of o-hydroxyphenyl-N-methylcarbamate

Data Evaluation Report (IX)

004231
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MRID 142731

Compounds:

2-isopropoxy-phenyl-N-methylcarbamate, BOQ 5812315, Propoxur, Baygon

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Study type:

Metabolism

Citation:

Eben, A. and Karl, W. Studies on the biotransformation of Propoxur in the rat. Report no. 12866, dated August 17, 1984. Control no. 88584. Study conducted at the Bayer AG EP-FE Institut für Toxikologie, Wupperta l-Elberfeld. Received at EPA 10-23-84; in Acc. 255177.

Reviewed by:

Byron T. Backus
Toxicologist
Toxicology Branch

Approved by:

Robert Zendzian, Ph.D.
Acting Section Head
Toxicology Branch

Core Classification: Supplementary

Conclusions:

1. The study is scientifically sound, and is of considerable interest as it demonstrates that the active ingredient is metabolized by a number of different pathways, and many (but not all) of the metabolites are identified. However, there is very little in the way of quantitative information. Also, the study is primarily concerned with the metabolites present in urine. As a result, the study satisfies no Agency data requirements.

Materials:

Test compound: Propoxur, 98.5-98.8% pure, batch no. 234101303. Reference compounds: 1,2-Dihydroxybenzene (VK 32-800, M1); 2-Isopropoxyphenol (VK 32-806, M2); 2-Hydroxyphenyl-methylcarbamate (THS 2490, M3); 2-Isopropoxyphenyl-carbamic acid (THS 1240, M4); 2-Isopropoxyphenyl-hydroxymethylcarbamate (THS 1241, M5).

Male Wistar rats BOR: WISW (SPF/Cpb) supplied by Winkelmann, Borchen, Kreis Paderborn.

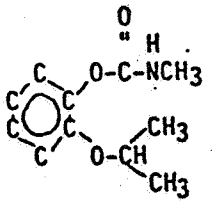
Procedure:

Groups of 10 male rats were maintained on a diet containing either 0 (controls) or 8000 ppm Propoxur. Thirteen weeks after the start of the study treated and control rats were placed singly in metabolism cages and the urine was collected for 24 hours. In order to avoid hydrolysis of some metabolites the pH of the urine was kept at between 4 and 5 by pipetting 0.5 mls 1N HCl into each receiver in the morning and afternoon.

According to the procedure given urine collected from 10 treated rats came to between 80 and 120 mls (interpretation is that the urine samples were pooled). There was a fairly lengthy extraction procedure, with analysis by thin-layer chromatography. Some compounds were identified by comparison with reference compounds, with verification by ^{1}H-NMR spectra and mass spectra. Other metabolites, for which no references had been prepared, had to be isolated and purified in quantities of 0.5-3 mg for identification.

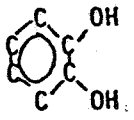
Results:

The test compound (Propoxur, structure given below) was identified in urine:

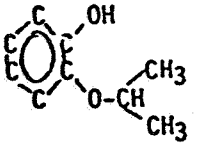


The following metabolites (structure shown below) were also identified in the urine, occurring either free, and/or as glucuronides and sulfates:

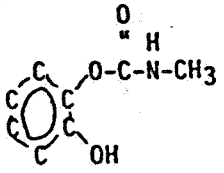
M 1 = 1,2-Dihydroxybenzene, pyrocatechol



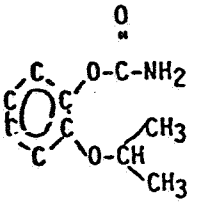
M 2 = 2-isopropoxyphenol:



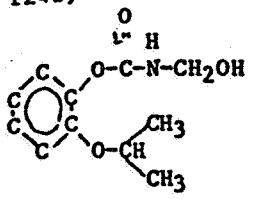
M 3 = 2-hydroxyphenyl methylcarbamate: (THS 2490)



M 4 = 2-isopropoxyphenyl-carbamic acid (THS 1240)

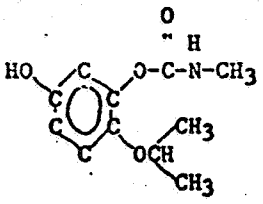


M 5 = 2-isopropoxyphenyl-hydroxymethylcarbamate
(THS 1241)

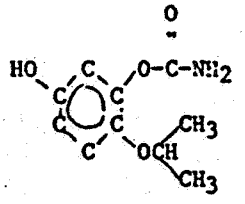


Note: This compound is identified as THS 1241b in some of the other studies.

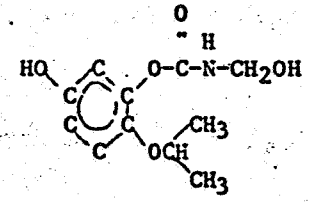
M 6 = 2-isopropoxy-5-hydroxyphenyl-methylcarbamate



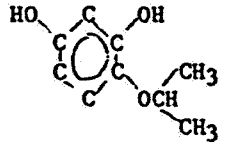
M 6 CII = 2-isopropoxy-5-hydroxyphenyl-carbamic acid



M S 3 = 2-isopropoxy-5-hydroxyphenyl-hydroxymethylcarbamate



M 7 = 1,5-dihydroxy-2-isopropoxy-benzene



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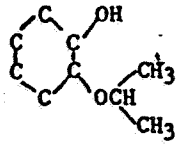
M 8 = 1,3-dihydroxy-2-isopropoxy-benzene



The report states (p. 48) that "No data can be given on the concentration of each metabolite."

In addition to the metabolites given above, the report states (p. 46) that several others were detected at very low concentrations, but that it had not been possible to isolate them.

Discussion:

The study is scientifically sound, although somewhat limited in scope. Because radioactive tracers were not used, it was not possible to get quantitative estimates as to how much of the active was metabolized, and how much of each metabolite was produced. The study does not satisfy any Agency data requirements.