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

OCT 28 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review Document on Propargite

FROM: Gary J. Burin, Ph.D., D.A.B.T.
Executive Secretary
Developmental/Reproductive Toxicity Peer Review Committee
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Sepehr Haddad, Review Manager
Special Review Branch
Special Review and Registration Division (H7508C)

The Health Effects Division Peer Review Committee (PRC) for Developmental Toxicity met on June 5, 1991 to discuss and evaluate the weight-of-the-evidence on propargite with particular reference to its potential for developmental toxicity. This was the second evaluation of propargite by the PRC. The Committee concluded that propargite induces developmental toxicity only at dose levels equal to or greater than those which also induce maternal toxicity. The most appropriate study for developmental toxicity risk assessment is the more recent study in the rabbit (IRDC, 1989) which has a NOEL for developmental toxicity of 8 mg/kg/day and a NOEL for maternal toxicity of 6 mg/kg/day.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Penelope A. Fenner-Crisp
William L. Burnam
Reto Engler
Karl Baetcke
Marcia Van Gemert

Gary J. Burin

Bob Sonawane

Thomas F.X. Collins

Jennifer Seed

Laurence D. Chitlik

Stephen Dapson

Roger Gardner

David Anderson

James Rowe

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

John Doherty

Marion Copley

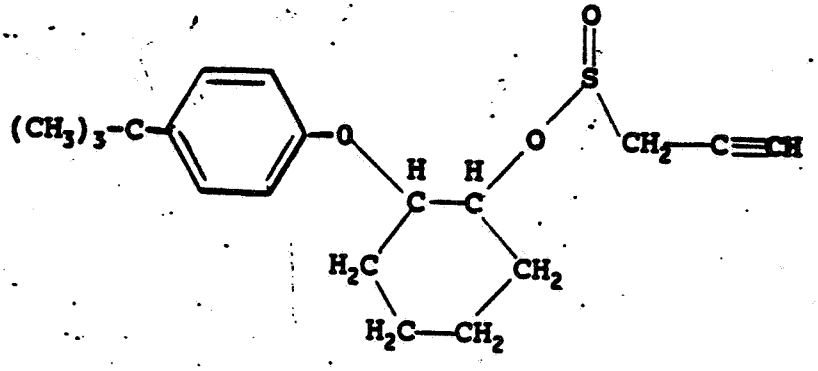
3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.).

Jennifer Orme

B. Material Reviewed:

The material available for review consisted of DER's, one-liners, and other data summaries prepared by Dr. John Doherty, the previous peer report and summary tables from the study reports. The material reviewed is attached to the file copy of this report.

Structure:



Structure of propargite.

C. Background Information:

Propargite is a broad spectrum acaricide used for the control of mites. It was the subject of a 1986 Registration Standard.

The first PRC meeting concerning the developmental toxicity of propargite was held on February 8, 1989. The data available to that PRC relevant to developmental toxicity consisted of two studies in which rabbits and rats were dosed during the period of major organogenesis and fetuses were examined after caesarian delivery. The peer review panel concluded that propargite induced developmental toxicity at levels above 2 mg/kg bw/day in the rabbit and that a NOEL for developmental toxicity could not be established in the rat. The effects considered to be treatment-related were identified as vertebral ossification delays in the rat and sternebral defects, resorptions and incomplete skull closure in the rabbit. The NOEL for maternal toxicity in the rabbit was 2 mg/kg and 6 mg/kg in the rat, both based on reduced body weight gain during the dosing period. Both studies were considered by the PRC to be "Supplementary" studies which would not support regulatory action. It was recommended that both studies be repeated.

The following are summaries of the studies in the rat and rabbit previously considered by the PRC.

1. "Teratologic Evaluation of Omite Technical in Sprague-Dawley Rats". Food and Drug Research Laboratories, Inc. Study #5992b, March 6, 1979.

Five groups of at least 20 pregnant Sprague-Dawley rats (BLU:(SD)BR) were dosed with either corn oil (vehicle control), aspirin (250 mg/kg in corn oil, positive control), 450, 105, or 25 mg/kg of propargite in corn oil. The volume of corn oil used was 10 ml/kg and the dams were dosed on days 6 through 15 of gestation. The high dose level of 450 mg/kg was terminated because of excessive deaths and a new low dose of 6 mg/kg was introduced into the study to ensure that a NOEL for maternal toxicity would be established. On day 20 of gestation, the females were sacrificed and their uterine contents assessed.

The PRC assigned a NOEL of 6 mg/kg/day and a LOEL of 25 mg/kg/day for maternal toxicity to this study based on body weight gain decreases during the dosing period. The Peer Review Committee concluded that the study did not demonstrate a definitive NOEL for developmental toxicity due to apparent increases in the occurrence of fetuses with incomplete ossification of the vertebrae at all dose levels receiving propargite.

2. "Teratology Study in Rabbits - Omite Technical" Hazleton Labs, #798-195, May 21, 1982.

Five groups of 17 pregnant New Zealand white rabbits were dosed with either vehicle control, 2, 6, 10 or 18 mg propargite/kg/day on days 6-18 of gestation. Corn oil was used as the vehicle and dosing was in a volume of 1 ml/kg by gavage. High mortality was observed in the dams of the 18 mg/kg/day dose level. The dams were sacrificed at day 29 of gestation.

The NOEL assigned for maternal toxicity by the 1989 Peer Review Committee report was 2 mg/kg/day based on reduced body weight gain observed at dose levels of 6 mg/kg/day and greater during the dosing period. For developmental toxicity, the previous PRC concluded that the NOEL was 2 mg/kg/day and the LOEL was 6 mg/kg/day based on an increased incidence of incomplete skull closure. At 10 mg/kg/day, increased incidences of resorptions and sternebrae defects were observed.

D. <u>Studies Pertaining to Developmental Toxicity Made Available Since the Previous Peer Review Meeting</u>

1. "Developmental Toxicity Study in Rats". International Research and Development Corporation, #399-096, January 5, 1990, MRID #413465-01.

Six groups of 45 pregnant rats (Sprague-Dawley, derived from the Charles River Crl:CD VAF/Plus strain) were dosed with either corn oil, (vehicle control), 6, 12, 18, 25, or 105 mg/kg/day of propargite technical by gavage on days 6 to 15 of gestation. The dosing volume was 4 ml/kg. At day 20 of gestation, the first 20 dams in each group presumed to be pregnant were sacrificed. The remaining dams were allowed to deliver their pups and these pups were monitored and raised through lactation to day 21.

The NOEL for maternal toxicity was 25 mg/kg/day and the LOEL 105 mg/kg/day based on anogenital and body surface staining and decreased body weight gain (with adjusted body weights decreased up to 5.5% compared to controls, $p < 0.01$). No developmental toxicity was observed at any dose level in the prenatal phase of the study.

In the postnatal phase, an increased number of litters with pup deaths (5/19 at 105 mg/kg bw/day compared to 0/19 in the control group) and an increased number of pups found dead (17/248 compared to 8/253) was found on day 0. The number of litters affected and the total number of dead fetuses at the high dose level was greater throughout lactation than that of controls or other dose levels (after the removal from consideration of one litter with 11 deaths at the 18 mg/kg dose level). However, an increase in pup mortality was not observed at other dose levels or after caesarian sacrifice in the prenatal study, live litter sizes

were similar between groups, there was no apparent increase in pup mortality after day 0 and pup body weights were similar in all groups. Statistical significance of the number of litters affected at the high dose level was only observed on day 7 ($p<.009$ by the Fisher's Exact test). See Section F, item 4 for a discussion of the PRC conclusions on this issue.

The incidence of litters with pup mortality on days 0, 3, 5 and 21 is shown in the Table 1.

Table 1. Incidence of Pup Mortality in Post-Natal Phase of Developmental Toxicity Study in the Rat (# of litters with deaths/ total litters)

Dose (mg/kg)	Day 0	Day 3	Day 5	Day 21
0	0/19	2/19	3/19	4/19
6	1/19	3/19	3/19	5/19
12	4/17	6/17	7/17	9/17
18	3/20	6/20	6/20	10/20
25	1/15	4/15	4/15	5/15
105	5/19	9/19	11/19	11/19

2. "Developmental Toxicity in New Zealand White Rabbits" International Research and Development Corporation (IRDC), #399-097, December 18, 1989.

Six groups of 25 pregnant rabbits were dosed with either 0 (vehicle control), 2, 4, 6, 8 or 10 mg/kg/day of propargite on days 7-19 of gestation. The vehicle was corn oil (1 ml/kg). The does were sacrificed on day 19 of gestation and fetuses examined externally, skeletally and viscerally.

The NOEL for maternal toxicity was considered to be 6 mg/kg/day and the LOEL 8 mg/kg/day based on decreased body weight gain during the period of dosing. The NOEL for developmental toxicity was recommended to be 8 mg/kg/day and the LOEL recommended to be 10 mg/kg/day based on an increased incidence of litters and fetuses with fused sternebrae. The incidence of litters with fused sternebrae at the high dose level was greater than that found in other studies conducted in this laboratory (a cumulative total of 26 of 415 litters in 29 studies were reported to have fused sternebrae with a maximum in any one study of 4 of 13 litters). Although increases in fused skull bones and accessory skull bones were noted in each of the 3 highest dose groups and the incidence

of these effects are at the high end of the historical control range, the low incidence of litters and fetuses with either of these findings and the absence of a dose-response precluded the determination that the incidences of fused or accessory skull bones were compound-related.

Table 2 presents the incidence of fused sternebrae, accessory skull bones and fused skull bones in fetuses and litters.

Table 2. Incidence of Selected Abnormalities in IRDC Rabbit Developmental Toxicity Study

Dose	0 mg/kg	2 mg/kg	4 mg/kg	6 mg/kg	8 mg/kg	10mg/kg
litters fetuses	17 106	15 101	17 121	18 139	18 125	16 116
fused sterne-brae	0 (0)*	2 (1)	1 (1)	0 (0)	2 (2)	9 (6)
fused skull bones	0 (0)	0 (0)	0 (0)	0 (0)	3 (3)	1 (1)
access. skull bones	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	1 (1)

* fetuses (litter)

3. Multi-generation reproduction study

The following is a description of a multigeneration reproduction study from the 1986 Registration Standard.

"A three-generation reproduction study was carried out with 25 male and 25 female rats fed 0 or 100 ppm propargite for one generation; the dose of the treatment group was increased to 300 ppm for the next two generations. The study results revealed no significant effects on either fertility or reproductive performance. Neonatal viability and lactation efficiency of the dosage group, as evidenced by the survival and growth of the young rats from birth to weaning, were comparable to that of the control group. Mean body weight of the pups was also comparable with the mean body weight of the control group. The NOEL is greater than 300 ppm. The study is considered as supplementary, as only one dose was used for each generation."

4. "Two Generation Reproduction Study with OMITE Technical in Rats (Two Litters per Generation)". Hazleton (Madison, Wisc.) #6111-108, January 9, 1990.

The design of this study consisted of dosing four groups of 25 male and 25 female rats with either 0, 80, 400 or 800 ppm of propargite. After a 10 week dosing period, the rats were bred to produce the F1a generation. After an additional 10 weeks, the rats were again bred to produce the F1b generation. The pups from the F1b generation were raised on their parental diets and the breeding procedure repeated to produce the F2a and F2b generations. The NOEL was concluded to be 80 ppm and the LOEL 400 ppm based on decreases in parental body weight and food consumption and decreases in pup weight during lactation. At 800 ppm, decreased mean pup birth weight was observed. No effects on other parameters were observed at any dose level.

E. Other Aspects of Toxicity

1. Acute Toxicity.

The acute oral LD_{50} in rats was determined to be 2.2 gm/kg. The acute dermal LD_{50} to rabbits was determined to be 3.16 gm/kg. The acute inhalation LC_{50} was determined to be > 2.5 mg/l for rats. Propargite was determined to be Toxicity Category I for both dermal and eye irritation.

2. Subchronic Toxicity.

The NOEL for a rat 90 day subchronic feeding study was determined to be 40 mg/kg/day (estimated equivalent to 400 ppm) based on retarded growth at 100 mg/kg.

A subchronic dermal toxicity study with rabbits indicated that propargite was an irritant at all dose levels including the lowest dose level tested (0.1 mg/kg/day). At the highest dose level tested (100 mg/kg/day) an increase in segmented neutrophils was noted. This may have been a response to the local dermal irritation.

3. Chronic Toxicity.

The NOEL for a dog chronic feeding study (dose levels of 0, 100, 300, and 900 ppm for three years) did not indicate adverse effects at any dose level (NOEL > 900 ppm). Data from two chronic feeding studies with rats indicate a NOEL of 900 ppm or greater. Body weight decreases and reduced food consumption were reported at the 2000 ppm dose level. Since neither study was acceptable, a chronic feeding study in rats was required in the Registration Standard.

4. Carcinogenicity.

A letter from the registrant regarding an ongoing chronic study indicates that rats in the high dose group (800 ppm) which died during weeks 65-77 of the study have masses which have been tentatively identified as undifferentiated sarcomas. None of the rats in the other groups were reported as having this tumor.

5. Mutagenicity.

The following is an excerpt from the Registration Standard.

"Propargite was tested for mutagenic activity in a series of in vitro microbial assays employing Salmonella and Saccharomyces indicator organisms. The compound was tested directly and in the presence of liver microsomal enzyme preparations for Aroclor-induced rats. The nonactivation and activation test results were all negative. Propargite did not induce any mutagenic activity in any of the assays conditions. Additional categories of mutagenicity testing are required for propargite."

6. Metabolism and distribution

The urine is the primary route of elimination in the rat following a low (25 mg/kg) oral dose (61% of the administered dose was eliminated by this route in males and 50% in females) over the course of 24 hours. The fecal route is the predominant route of elimination in both sexes following a high dose (200 mg/kg) with about 70% of the administered dose eliminated by this route. The biliary route is a minor route of elimination in the rat (6.1%), rabbit (0.02%) and monkey (0.7%). The respiratory air is also a minor route of excretion following an oral dose (52 mg/kg) since only 0.03% (males) and 0.04% (females) of dose was eliminated by this route. Only a small amount (1.6%) of test compound is retained in tissues after 24 hours. Highest levels of test material were detected in the liver, kidneys and gastrointestinal tract. Similar findings were noted in a second rat study and in studies with rabbits and monkeys.

Metabolism includes hydrolysis of the sulfur-oxygen bond to yield propynyl sulfite and the substituted cyclohexyl structure. This structure is further hydroxylated (hydroxylation may occur prior to hydrolysis), conjugated and eliminated. The tertbutyl substituted of the phenoxy moiety is also hydroxylated to alcohol and carboxylic acid structures.

7. Structure Activity relationships.

No information on structure activity relationships was found in a computerized search.

F. Issues and Recommendations

1. The Committee recommended that a NOEL for developmental toxicity in the second rabbit study be established at 8 mg/kg/day based on an increased incidence of litters with sternebral defects (fused/malaligned sternebrae) at 10 mg/kg/day. The NOEL for maternal toxicity in this study is 6 mg/kg/day based upon decreased body weight gain during the dosing period. This study was considered to be of better quality than the initial study (see previous Peer Review) and the NOEL from this second study in the rabbit was therefore considered to be more useful for risk assessment purposes.

2. The Committee concluded that the recently submitted developmental toxicity study in the rat (which included a postnatal phase) did not support the previous association of ossification defects with test compound administration. The overall quality of the second study was considered to be better than that of the first study (see previous Peer Review).

3. The Committee agreed that the NOEL for maternal toxicity in the second developmental toxicity study in the rat is 25 mg/kg/day (LOEL=105 mg/kg/day) based on anogenital staining and decreased body weight gain.

4. The Committee was evenly divided regarding the biological significance of the increased pup mortality observed at the highest dose level in the postnatal phase of the rat developmental toxicity study. The association of compound administration with increased pup mortality at the high dose level was supported by the increased number of litters with pup deaths and increased number of fetuses found dead on day 0. These differences in numbers of litters and fetuses affected at the high dose level remained throughout gestation. Committee members who did not consider this observation to be compound-related noted the lack of increase in pup mortality after day 0, similar pup body weights in all groups, similar numbers of live pups per litter in all test groups and the absence of other evidence of developmental toxicity in this study. Statistical significance of the number of litters affected at the high dose level was only observed on day 7 ($p<.009$ by the Fisher's Exact test).

Note bene: even if the increase in pup mortality was considered to be biologically significant, the overall NOEL for this study (25 mg/kg) and the overall NOEL for developmental toxicity (8 mg/kg in the rabbit) remain unaffected.

5. Regarding the multigeneration reproduction study, the Committee concluded that the available data indicated that body weight gain was adversely affected during lactation in both the dam and pup at dose levels of 400 and 800 ppm (20 and 40 mg/kg/day). The NOEL for this study was determined to be 80 ppm (4 mg/kg). The

Committee recommended not attempting to differentiate in this study between effects on the pups which may have been induced in utero from those that may result from systemic toxicity to the pups due to exposure via lactation.

G. Conclusions

Developmental toxicity previously identified in the form of sternebral defects was confirmed in a second study in the rabbit. The NOEL for this effect is 8 mg/kg/day, a level which also induces maternal toxicity. This NOEL should be compared to likely human exposure for the purpose of developmental toxicity risk assessment. Propargite induces only equivocal developmental toxicity in the rat at dose levels which also induce maternal toxicity (105 mg/kg/day).