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

APR 26 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

To: John H. Lee, Product Manager #31
Registration Division (TS 767C)

Thru: Judith Hauswirth, Ph. D., Section Head
Review Section 6
Toxicology Branch
Hazard Evaluation Division (TS 769)

Judith W. Hauswirth 4/21/88

From: Roger Gardner, Toxicologist
Review Section 6
Toxicology Branch
Hazard Evaluation Division (TS 769)

Roger Gardner 4-21-88

4/24/88

Subject: New Uses for Myacide AS Plus (EPA Reg. No. 33753-5). Tox. Chem. No. 116A (Tox. Project No. 8-0581).

Action Requested

Registration of Myacide AS Plus for industrial uses as an in-can preservative for surfactants, raw materials (perfumes, detergents, etc); consumer, household, and institutional products; paints, pigments and extender slurries; water-based agricultural pesticide concentrates; latex and antifoam emulsion systems; water-based adhesives, printing inks; and other similar in-can uses.

Recommendations and Conclusions

1. The requirement for a teratology study in one species is not satisfied by the availabe studies (see Sections I. B., I. C. 4., and II. below).

2. The requirement for mutagenicity studies is not satisfied by the available data (see Sections I. B., I. C. 6., and II. below).

3. There is no information on whether the proposed uses will result in frequent exposure to respirable droplets or particles (15 microns or less in diameter). Therefore, a 90-day inhalation study or information on the respirability of the formulation is required.

4. Because of the data gaps listed in points 1., 2., and 3. above, the proposed new uses are not toxicologically supported.

I. Background

A. Uses and Formulation

Bronopol (2-bromo-2-nitropropane-1,3-diol) is a biocide registered for use as an industrial preservative to prevent bacterial degradation of water-based adhesives, paints, latex emulsions and inks, pigment slurries, and metalworking fluids. In addition to the uses already registered, the biocide is proposed for use as an in-can preservative for surfactants, raw materials (perfumes, detergents, etc); consumer, household, and institutional products; and water-based agricultural pesticide concentrates.

The formulation proposed for these uses is Myacide AS Plus (containing 95% active ingredient).

B. Exposure Considerations

The Registrant's submission provided recommended conditions of use as follows:

> Myacide AS Plus may be added at any convenient point during the manufacturing process for the product concerned. Ideally it should be added as a final step just prior to packing of the product into bulk or sales packs.
>
> QUANTITY
>
> Myacide AS Plus should be added to a dose of 100 to 500 ppm based on the final formulation volume...

The Agency classifies the proposed industrial uses of antimicrobials like bronopol into the "low exposure" category (see "Toxicology Data Call-In for Antimicrobial Pesticides." dated January 7, 1987, Federal Register Vol. 52, No. 4; and "Data Call-In Notice for Subchronic and Chronic Toxicological Data for Antimicrobial Pesticide Active Ingredinets." Attachment A, Table 1). Toxicology data requirements for the proposed uses are based on exposure and a tier system with minimum requirements (Tier 1 testing) that can be as follows:

Study	Guideline No.
A 90-day dermal study	§82-3
A 90-day inhalation study	§82-4
A teratology study (one species)	§83-3
Mutagenicity studies	§82-4

Additional data requirements (Tiers 2 and 3) are contingent upon results of the Tier 1 tests.

C. Summary of Existing Toxicity Data

The Toxicology Branch has previously reviewed the data discussed in this Section (see Gardner, 1983 and 1984, and Appendix II. below).

1. Acute Toxicity

The Toxicity Categories indicated for the technical grade material and a 10% formulation (Bronacide 10A: 10% a. i.) are summarized as follows:

Type of Study	Toxicity Category	
	Technical	Bronacide 10A
Acute oral toxicity	II	III
Acute inhalation toxicity	III	III
Acute dermal toxicity	III	III
Primary eye irritation	I	III
Primary skin irritation	I	III

The acute dermal LD_{50} value for the technical grade material was based on use of 2 rats per dose group, and the results were considered along with those from other studies with diluted test substance to determine the Toxicity Category. Undiluted technical grade bronopol is corrosive and is therefore classified into Toxicity Category I with respect to its eye and skin irritation potential.

No skin sensitization was observed in guinea pigs for the technical grade material, but Bronacide 10A was found to be a sensitizer.

2. Subchronic and Chronic Toxicity

No-observed-effect levels (NOEL) (mg/kg/day) and lowest effect levels (LEL) with respect to body weight decreases or mortality are summarized as follows:

Study	NOEL	LEL
13-week rat gavage study	20	80
13-week dog study*	4	8
2-year rat study**	10	40

*Liver and spleen weight increases were observed
**Test substance was administered in the drinking water

Effects observed in rats given the 40 mg/kg/day dose for two years were gastrointestinal irritation, decreased food consumption, and increased mortality.

3. Oncogenicity

Bronopol did not induce tumors at 40 mg/kg/day administered in the drinking water in the long-term rat study mentioned above.

A long-term mouse study indicated that bronopol is not oncogenic under the test conditions (dermal application of up to 0.5% active ingredient).

4. Teratology

a. Rats

In one supplementary teratology study doses of 0, 10, 30, or 100 mg/kg/day were administered by gavage on days 1 through 20 of gestation. The results indicated that the NOEL for maternal toxicity in rats (mortality) was below 10 mg/kg/day.

Although no fetal effects were observed in this study, the test substance was administered prior to implantation.

In a second study, two groups of pregnant rats were given 0 or 10 mg/kg/day by gavage on gestation days 15 through 21. The dams were allowed to nurse their offspring. There was no mortality observed in treated dams, and one of the treated dams was sacrificed on day 19 of lactation because of poor condition. Fetuses were not examined prior to delivery in this study, and dosing was not conducted during the period of major organogenesis.

When oral doses of 0, 20, or 40 mg/kg/day were given to pregnant rats from day 15 to day 21 of gestation, no maternal mortality or fetal effects were observed. However, the doses were not administered during the period of major organogenesis as in the second study described above.

These three studies followed protocols that are not comparable to each other or to those recommended by the Agency (Pesticide Assessment Guidelines. Subdivision F. Hazard Evaluation: Human and Domestic Animals. §83-3. Office of Pesticide Programs, U. S. EPA. November, 1982.). Two of the three studies did not evaluate effects of the compound during the period of major organogenesis (days 6 through 15 of gestation), and the doses used in the first and third studies caused maternal mortality. Taken together these three studies suggest that the NOEL for maternal toxicity (mortality) in pregnant rats is less than 10 mg/kg/day for bronopol administered orally during the first two-thirds of gestation (days 1 through 15).

In a fourth study. pregnant rats were given 0, 20, or 40 mg/kg/day by dermal application on days 6 through 15 of gestation, and the only effect in treated animals was dermal irritation. There were no fetal effects reported in treated rats. Although a dermal absorption study in rats suggested that bronopol is capable of dermal penetration, no systemic effects were observed in the dermal teratology study to indicate that sufficiently high doses were tested. In view of the dermal irritation caused by bronopol (see Section I. B. 1. above), the dermal route may not be appropriate in an evaluation of the chemical's potential to cause developmental toxicity.

These considerations as well as the specific deficiencies of the protocols described above indicate that bronopol's potential to cause developmental toxicity has not been completely evaluated in the rat, and additional testing would be required when exposure is considered.

b. Rabbits

No effects were observed on the fetuses of rabbits given 0, 1, 3.3, or 10 mg/kg/day on days 6 through 16 of gestation. A decrease in maternal body weight gain was noted at the 10 mg/kg/day dose level, but there were no significant differences with respect to group mean body weights during gestation. However, this study provides supplementary information because insufficient numbers of animals were used in each test group to detect significant differences for some observations.

5. Reproductive Effects

Reproduction studies were submitted, but they have not been reviewed for the following reasons:

a. One of the two studies used only one dose and produced one generation of offspring.

b. The other study only used two doses and one generation of offspring from approximately half the animals needed in a standard study.

6. Mutagenicity

Results of unacceptable in vitro and host mediated microbial assays suggested that bronopol is not mutagenic in Salmonella typhimurium. In addition, the use of bronopol as an antimicrobial agent suggests that the chemical's toxicity to microbial organisms compromises their usefulness in the evaluation of bronopol's potential to cause genotoxic effects in humans.

An unacceptable dominant lethal study in mice suggests that bronopol may have an effect on germ cells in males. In view of the potential germ cell effects suggested by the results of this study, there is a need for a more appropriate battery of assays which will characterize the biocide's potential to cause gene mutations, chromosomal damage, or other related effects (e. g., primary DNA damage).

7. Metabolism

Several metabolism experiments indicate that rats and dogs rapidly absorb oral doses of 1 or 2 mg bronopol per kg body weight. The chemical is excreted primarily in the urine (approximately 80-85% in 24 to 120 hours after dosing). The feces and expired air are also routes of excretion.

A rat study demonstrated that dermal penetration of Bronopol is 4 to 10% (recovered in the urine over a 5-day period following treatment) at a concentration of 4 mg/ml. A second dermal experiment (tissue distribution) demonstrated that 11% of the applied dose was excreted in the urine during the 24 hours following treatment, and the majority of the dose was found in the skin of the test site.

Bronopol does not accumulate in any particular organ, and the tissues with the highest residue concentrations are involved in excretion (liver, kidneys, and lungs).

II. Discussion

A 90-day dermal toxicity study is not required for bronopol since Myacide AS Plus is a corrosive material. In addition, there are 90-day feeding studies, dermal absorption studies, and acute oral and dermal studies available that satisfy the requirement as stated in the Data Call-In Notice cited in Section I. B. above.

Although Myacide AS Plus is not a gas, there is no information on whether its use will result in respirable droplets or particles (15 microns or less in diameter).

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Therefore, a 90-day inhalation study or information on the respirability of the formulation is required.

The teratology studies (see pages 3 and 4 above) do not satisfy the requiremnt for a study in one species. Therefore, a teratology study is needed to support the proposed new uses.

Circumstances of bronopol's toxicity (see Section I. C. 6. above) suggest that additional mutagenicity assays are needed. These assays should evaluate the chemical with respect to gene mutation, chromosomal damage, and other genotoxic effects, and the Agency should be consulted on appropriate tests to satisfy the requirement.

III. References

Gardner, R. Memorandum dated October 6, 1983. Subject: Review of toxicology data on bronopol. EPA Reg. No. 47374-R. Tox. Chem. No. 116A. To: J. Lee, Registration Division.

Gardner, R. Memorandum dated December 3, 1984. Subject: Review of acute toxicity studies on Bronacide 10A and additional information on previously submitted studies. EPA Reg. Nos. 47374-E and 33753R. Tox. Chem. No. 116A. To: J. Lee, Registration Division.