00774

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: California Department of Food and Agriculture - EPA Toxicology Review for Cryolite.

Tox. Chem. No. 264

TO: William Burnam, Acting Division Director
Health Effects Division (TS-769c)

FROM: Yiannakis M. Ioannou, Ph.D.
Section 2, Toxicology Branch I (IRS)
Health Effects Division (TS-769c)
Y.M. Ioannou 1-17-89

THRU: Marion Copley, D.V.M. Acting Head
Section 2, Toxicology Branch I (IRS)
Health Effects Division (TS-769c)
Marion Copley 1/18/89

The following responses are provided for each specific deficiency identified by the Medical Toxicology Branch of the California Department of Food and Agriculture:

STUDY TYPE: Teratology - Rabbit

Deficiency: No Study on file

EPA Response: As stated in the Registration Standard for Cryolite, issued by the Agency in April 1988, the requirement for a teratology study in rabbits was waived based mainly on the fact that Cryolite at very high dose levels (up to 3,000 mg/kg/day) did not induce any toxic or teratogenic effects in a rat teratology study.

The decision by the Agency to waive the requirements for the teratology study in the rabbit appears to have been inappropriate, considering that EPA Guidelines specify that teratology studies should be conducted in two mammalian species (usually rat and rabbit).

CONCLUSION: We concur with CDFA; the teratology study in rabbits remains a data gap.

cc Burnam

STUDY TYPE: Mutagenicity - Gene Mutation Assay - #T1693.102; September, 1981.

Deficiency: No confirming repeat trial

EPA Response: At the time of the conduct of this study (1981), no official guidelines existed to allow for a uniform conduct of all toxicity studies, and thus the registrant might have failed to perform a repeat test in the gene mutation assay. Based on current EPA guidelines however, this deficiency would have resulted in an unacceptable study.

CONCLUSION: We concur with CDFA; this study remains a data gap.

CLASSIFICATION: Unacceptable. change to !

STUDY TYPE: Mutagenicity - In Vivo Cytogenetic Assay in Rodents - #T1693.112; September, 1981.

Deficiency #1: The Registrant did not justify as to why only male rats were used for this assay.

EPA Response: At the time of the conduct of this study (1981), no official guidelines existed to require the conduct of this study in both sexes of rats. However, this deficiency, coupled with the use of only 5 animals, can account for classifying this study as unacceptable.

Deficiency #2: The Registrant should provide historical control data.

EPA Response: Based on the data reported here, only cells treated with TEM (positive control) showed severe cell damage. None of the cells from the vehicle control group (corn oil) of the cryoside-treated groups showed any damage. Thus, historical control data would not serve any purpose in evaluating this study.

CONCLUSION: We concur with CDFA with respect to deficiency #1.

CLASSIFICATION: Study should be Unacceptable not acceptable

STUDY TYPE: Mutagenicity - DNA Repair Assay Using E. Coli - #T1693.104; September, 1981.

Deficiency: No cytotoxicity was observed in either strain; the highest dose tested was not high enough.

EPA Response: EPA raised this point in the initial review of this study. The Registrant submitted additional data to the Agency concerning mainly purity and stability of cryocide, but no justification for the low dose levels tested.

CONCLUSION: We concur with CDFA that this was "No test" and this study remains a data gap.

CLASSIFICATION: Change to Unacceptable.

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Note to: Judy Hauswirth

SUBJECT: Responses to CDFA on Cryolite

Based on my reading of page 10 of the 1988 revised registration standard on cryolite, I have found that the data waiver for the teratology study in the second species (rabbit) was based on judgment, general knowledge of the toxic effects of this type of chemical and the results of the rat teratology study. I found it difficult to consider this waiver "inappropriate" based only on a reference to our EPA Guidelines. I believe this waiver should stand as is.

cc: Bruce Jaeger

1/23/89

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United States
Environmental Protection
Agency

Office of
Pesticides and Toxic Substances
Washington DC 20460

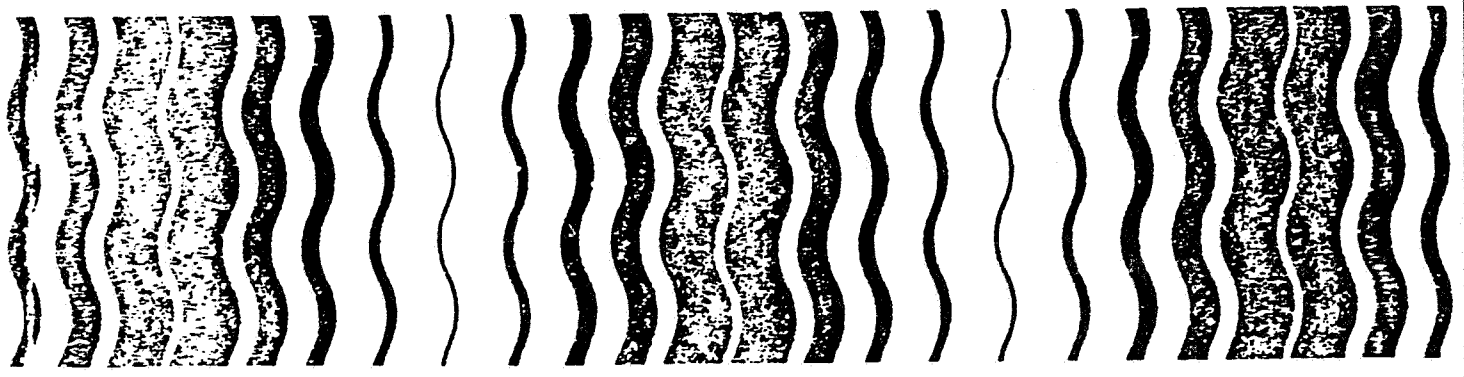
007744

540-RG-88-069

Pesticides

EPA

Guidance for the Reregistration of Pesticide Products Containing CRYOLITE as the Active Ingredient



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study, the lowest doses tested. Cryolite NOELs for other effects were 50 ppm (2.5 mg/kg) in the rat (stomach lesions[4] at 5000 ppm) and 10,000 ppm (250 mg/kg) in the dog (decreased body weight, decreased body weight gain, decreased food consumption, and a decrease in hematological parameters at 50,000 ppm).

3. Chronic Toxicity Testing

In the 1983 Cryolite Registration Standard, the Agency required submission of a rat teratology study and mutagenicity data. Requirements for chronic feeding, oncogenicity, a teratology study in a second species, and a reproduction study were reserved pending submission and review of the data required in the 1983 Standard, specifically the 90-day subchronic feeding studies, rat teratology study, mutagenicity studies, and residue data. A metabolism study was not required, since there were acceptable data on file to support registration of cryolite products. Data submitted in response to the 1983 Cryolite Registration Standard are discussed below.

84-4 - Mutagenicity

Acceptable mutagenicity studies have been submitted to support registration of cryolite products. Technical cryolite tested negative for mutagenic activity in a Salmonella/Microsomal Assay (Ames). It was also negative in a DNA repair test using Escherichia coli for genotoxic effects and in a rat in vivo cytogenetics assay for structural chromosome aberrations. No further testing is required.

83-3 - Teratogenicity

An acceptable rat teratology study has been submitted to support registration of cryolite products. In this study, cryolite was tested in rats at dosage levels of 750, 1500, and 3000 mg/kg. Cryolite did not demonstrate a teratogenic potential at doses up to and including 3000 mg/kg, and was not shown to be fetotoxic. A whitening of the dam teeth in treated animals was the only change in either dams or fetuses that was attributable to cryolite treatment. The No Observed Effect Level (NOEL) for maternal and fetotoxicity is 3000 mg/kg (highest dose tested). Based on the negative findings in the rat teratology study, coupled with the high dose levels tested, the Agency is not requiring a rabbit teratology study.

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[4] Stomach lesions such as thickened wall, raised focal area, inflammation, hyperkeratosis, acanthosis.

007744

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CRYOLITE

SB 950-056, Tolerance #145

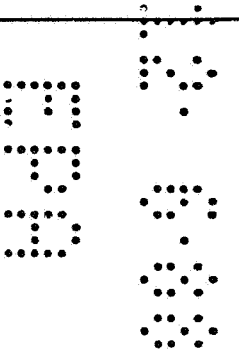
November 17, 1986
Revised: September 3, 1987
Revised: July 6, 1988

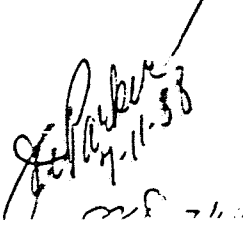
I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study on file
Chronic toxicity, dog:	Data gap, no study on file
Oncogenicity, rat:	Data gap, no study on file
Oncogenicity, mouse:	Data gap, no study on file
Reproduction, rat:	Data gap, no study on file
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	Data gap, no study on file
Gene mutation:	Data gap, inadequate study, no adverse effect indicated
Chromosome mutation:	Data gap, inadequate study, no adverse effect indicated
DNA damage:	Data gap, inadequate study, no adverse effect indicated
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T880706
Revised by Kishiyama & Davis, 7/6/88





Document 145-013, dated June, 1983, contains the EPA Registration Standard for this compound and identifies data gaps in all required toxicology study categories i.e., chronic toxicity, oncogenicity, teratogenicity (partial for rat), reproduction, and all mutagenicity study types. EPA determined that it should continue to allow the registration of cryolite, provided that registrants provide or agree to develop additional data, for the following reasons:

1) No toxicological hazards of concern have been identified from the studies reviewed, and the sequential testing approach is being used because the chemical properties of this compound are unique.
2) Data show that the public is not being exposed to over tolerance residue levels.
3) Data from tests required by registration guidelines would not be meaningful.
4) Existing studies suggest low toxicity to wildlife; more studies are requested.
5) Human poisoning incidents appear to be from misuse or accident.
6) EPA cannot withhold registration because data are missing or inadequate.

Gaps in the data base preclude completion of the Agency's risk assessment on this chemical. EPA has deferred its reassessment of this compound until essential data on residues and toxicology tests are available.

Reference to the wealth of available toxicological literature on fluoride is made including "other toxicity data previously submitted on cryolite, such as a teratology study in rats,... and ...mutagenicity tests". CDFA now has these studies on file (September, 1987).

019 43856 "The Registrant's Justification for Exemption from Tolerance Submitted in Conjunction with Data Required under the Cryolite Registration Standard of June 28, 1983". Dated March 1986. Additionally, three subchronic studies were submitted in support of registration. One-liners from these studies are below.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

SUBCHRONIC (SUPPLEMENTAL)

SUBCHRONIC, RAT

022 043859 "Subchronic Toxicity Study with KRYOCIDE Insecticide in Rats" (Hazelton Laboratories America, Inc., study no. 6120-100, 1/27/85) : Cryolite, 96% pure, fed at 0, 50, 5000 and 50,000 ppm in diet to 40, 40, 40, and 50 CD (SD) BR rats/sex, respectively (20 "core animals", 10 satellite animals for clinical chemistry and hematology; interim sacrifices preinitiation, days 7, 15, 45, 90, 128); **POSSIBLE ADVERSE EFFECT**-Anemia; microscopic findings in kidney, stomach, bone, and incisors. McGee 9/26/86. NOEL = 50 ppm (based on supplemental histopathology in Records 065012 & 067215); Kashiyama & Davis 7/5/88. **SUPPLEMENTAL STUDY**-acceptability in lieu of a chronic study will be considered once the conclusions of EPA have been received and evaluated by Medical Toxicology (see the report of the 1/27/88 meeting).

028 065012 Preliminary histopathology data on stomachs and incisors from 022 043859.
029 067215 Final Report Amendment No. 1 (histopathology data on stomachs and incisors from 022 043859.

SUBCHRONIC, DOG

021 043858 "90-Day Dietary Study in Dogs with Kryocide" (WIL, Report # WIL-75007, 1/18/86) Cryolite (97.3%) at 0, 500, 10,000 or 50,000 ppm fed to 6 (8 high dose)/sex/group, interim sac @ 0, 45 days and 28 day recovery period (high dose only). NO ADVERSE EFFECT-Decreased RBC, Hb, Hct, and RBC morphology changes at 50,000 ppm (extremely high-5% of diet). Plasma, urine and bone fluoride concentrations were dose related. Partial recovery during recovery period, except for sternal fluoride. NOEL = 10,000 ppm (35 mg/kg day). Reviewed as ACCEPTABLE (McGee 9/26/86); SUPPLEMENTAL STUDY (Kishiyama & Davis 7/6/88)

020 043587 "28 Day Dietary Study in Dogs with Kryocide" (WIL, Report # WIL-75010, 7/25/85) Cryolite, (97.3%) fed at 0, 500, 10,000 or 50,000 ppm for 28 days, 1 dog/sex/dose. Effect: 50,000 ppm female lost weight, had a decrease in food and water consumption, 60,000 ppm female was comparable to control. Urine and plasma flouride levels increased in a dose-related manner though 50,000 ppm female value exceeded those of the 60,000 ppm female. McGee 9/24/86.

CHRONIC TOXICITY, RAT

No study on file.

CHRONIC TOXICITY, DOG

No study on file.

ONCOGENICITY, RAT

No study on file.

ONCOGENICITY, MOUSE

No study on file.

REPRODUCTION, RAT

No study on file.

TERATOLOGY, RAT

**025 059221 "Final Report for a Teratology Study of Kryocide Insecticide in Albino Rats" (Science Applications Inc., Study No. 1182008, 3/17/83) Kryocide (lot 86-11-9, purity of 97.6% from record # 59217.10 025) given by oral gavage to 30 per group at 0, 750, 1500, or 3000 mg/kg, days 6 - 19 of gestation, (SD) fBR rats; only clinical observation was whitening of the dams' teeth starting around day 16 or 17 of gestation; NO ADVERSE EFFECT-no developmental toxicity or maternal toxicity reported; maternal and developmental NOELs $\geq$ 3000 mg/kg/day - FIFRA states that 1000 mg/kg/day is an acceptable high dose for relatively non-toxic chemicals. ACCEPTABLE. Gee 8/31/87

TERATOLOGY, RABBIT

No study on file.

GENE MUTATION

025 059217, 059218 "Activity of Kryocide in the Salmonella/microsome Assay for Bacterial Mutagenicity" (Microbiological Associates, Study T1693.102, 9/29/81) Kryocide (97.5%) tested in Salmonella strains TA1535, TA1537, TA1538, TA98, and TA100 with and without rat liver activation (Aroclor 1254-induced) at 0, 0.05, 0.15, 0.50, 1.5 and 5.0 mg/plate in triplicate, single trial. **UNACCEPTABLE** (no confirming repeat trial.) Gee 8/27/87

EPA 1-liner: A separate repeat test not performed. No tox. test conducted to determine suitable doses. Chemical characterization of the material not reported. Core Grade Unacceptable.

CHROMOSOME MUTATION

025 059220 "Activity of T1693 in the in vivo Cytogenetics Assay in Rodents" (Microbiological Associates, Study Number T1693.112, 10/2/81) Kryocide (96%) given by oral gavage to 5 males per group at 0, 0.6, 1.8, or 6.0 gm/kg body weight/day for five consecutive days; sacrificed 4 hours after the last dosing; TEM as positive control; 50 metaphase cells scored per animal and the mitotic index determined for each animal; **NO ADVERSE EFFECT** on chromosomes is reported. Study is **UNACCEPTABLE** but possibly upgradeable with justification of using only males and submission of historical control data. Gee 8/28/87

EPA 1-liner: Test chemical not characterized. No demonstrable toxic effects at the highest dosage reported. Insufficient dosage may have been administered to the rats. No assurance was made that the test article was absorbed from the G.I. tract. Core Grade Unacceptable.

DNA DAMAGE

025 059219 "Activity of T1693 in a DNA Repair Test using Escherichia coli - Final Report" (Microbiological Associates, Study Number T1693.104, 9/21/81) Kryocide (96%) disk assay in Escherichia coli strains W3100/polA$^+$ and p3478/polA$^-$, with and without rat liver activation at 0, 0.1, 0.3, or 1.0 mg/disk in 20 ul DMSO, in triplicate, single trial. **UNACCEPTABLE** (no cytotoxicity in either strain = no test.) Gee 8/27/87

EPA 1-liner: Inconclusive: 1) the highest dose may not have been used. 2) Solubility data were not provided. 3) Chemical characterization of the test chemical was not included. Core Grade Unacceptable.

NEUROTOXICITY

Not required at this time.

LITERATURE REVIEW (SUPPLEMENTAL)

028 065013 "Updated Literature Review. Fluoride Metabolism and Toxicity" This review is of minimal utility because it is unsigned and undocumented by references. No worksheet done. Davis 7/5/88

7/11/88

7/6/88