CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Halofenozide

Chemical Code #: 5019 **Tolerance** # 52123
SB 950 N/A

Date: 4/23/10

I. DATA GAP STATUS

Chronic toxicity, rat: Data gap, no study on file[a].

Chronic toxicity, dog: Data gap, no study on file[a].

Oncogenicity, rat: Data gap, no study on file[a].

Oncogenicity, mouse: Data gap, no study on file[a].

Reproduction, rat: Data gap, no study on file[a].

Teratology, rat: No data gap, no adverse effect indicated.

Teratology, rabbit: No data gap, no adverse effect indicated.

Gene mutation: No data gap, no adverse effect indicated.

Chromosome effects: No data gap, no adverse effect indicated.

DNA damage: No data gap, no adverse effect indicated.

Neurotoxicity: No data gap, no adverse effect indicated.

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[a] Halofenozide has been submitted and classified as a non-food use for purpose of toxicological data requirements for USEPA and is considered of low priority in risk assessment consideration. No further studies are required at this time to satisfy SB950 data requirements for halofenozide.

Toxicology one-liners are attached.

All record numbers through 149230 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T100423
Revised by R. Pan, 4/23/10

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

No study on file.

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

** 018 149223 "Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of RH-70, 345 Administered Orally Via Gavage to Crl:CDBR VAF/Plus Presumed Pregnant Rats", (Foss, J.A., Argus Research Laboratories, Horsham, PA, Study #: 93P-083, March 4, 1994). Halofenozide (RH-70,345; 91.7% pure) was administered by gavage to Crl:CDBR VAF/Plus presumed pregnant rats (25/dose) at 0, 5, 30 or 180 mg/kg during days 6-15 of gestation. Maternal NOEL = 30 mg/kg/day (At 180 mg/kg/day, death, significantly decreased body weight and body weight gain and food consumption were observed.) Developmental NOEL = 30 mg/kg/day (At 180 mg/kg/day, fetuses had significantly decreased body weights and decreased numbers of ossified caudal vertebrae and forelimb metacarpals.) **No adverse effect. Acceptable.** M. Silva, 4/29/97.

TERATOLOGY, RABBIT

** 019 149224 "RH-70, 345 Technical: Oral (Gavage) Developmental Toxicity Study in Rabbits," (Danberry, T.L. and Shuey, D.L.; Rohm and Haas, Philadelphia, PA; Protocol #: 94P-015 and Report #: 94R-015; 4/4/95). Halofenozide (RH-70,345; 91.7% pure) was administered by gavage to mated New Zealand White rabbits (17/dose) at 0, 10, 20, 60 or 180 mg/kg/day during days 7-19 of gestation. Maternal NOEL = 10 mg/kg/day (At $\geq$ 20 mg/kg/day, tremors were observed. At 60 and 120 mg/kg/day, there were increased clinical observations, deaths, abortions and decreased body weight gain and viable litters at sacrifice. The percent methemoglobin was significantly increased at 60 and 120 mg/kg/day. There was a decreased RBC and platelet count at 120 mg/kg/day.) Develop- mental NOEL = 120 mg/kg/day (There were no treatment-related effects observed at any dose.) **No adverse effect. Acceptable.** M. Silva, 4/30/97.

GENE MUTATION

** 020 149227 "RH-70, 345: Salmonella Typhimurium Gene Mutation Assay (Ames Test)",

(Sames, J.L. and Elia, M.C.; Rohm and Haas, Philadelphia, PA; Report #: 94R-0019; 11/21/94). Halofenozide technical (91.7% pure) was evaluated in a gene mutation assay (Ames test) with Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 at 0, 20, 50, 200, 500 and 2000 ug/plate both with and without S9 (triplicate plates). A repeat test was performed with the same bacterial strains (+/-S9) at 0, 125, 250, 500, 750 and 1000 ug/plate (triplicate plates). There was no treatment-related increase in gene mutation at any dose. The appropriate positive controls responded as expected. **Acceptable. No adverse effect.** (M. Silva, 5/1/97).

** 020 149228 "Test for Chemical Induction of Gene Mutation at the HGPRT Locus in Cultured Chinese Hamster Ovary (CHO) Cells With and Without Metabolic Activation", (Pant, K.J., SITEK Research Laboratories, Rockville, MD; Report #: 92RC-0202; SITEK Study #: 0226-2500; March 10, 1994). Halofenozide technical (97.8% pure) was tested in a gene mutation assay with the HGPRT Locus with CHO cells (+/-S9) 0, 0.49, 0.99, 4.9, 9.9, 49 or 99 ug/ml (duplicate plates; 5 hour exposure). Two definitive studies were performed along with parallel toxicity tests. Tests were negative for gene mutation. Positive controls functioned as expected. **Acceptable. No adverse effect.** (M. Silva, 5/2/97).

CHROMOSOME EFFECT

** 020 149229 "Test for Chemical Induction of Chromosome Aberration Using Monolayer Cultures of Chinese Hamster Ovary (CHO) Cells With and Without Metabolic Activation", (Kumaroo, P.V., Sponsor's report #: 92RC-203; SITEK Research Laboratories; April 5, 1994). Halofenozide technical (97.8% pure) was tested in a chromosome aberration assay with CHO cells (+/-S9) at 0, 13, 25, 50, 100 and 150 ug/ml. With S9 exposure was for 2 hours and without S9 exposure was for 12 and 22 hours (duplicate cultures/dose/time point). The definitive test was repeated. A parallel toxicity test was performed. Positive controls functioned as expected. **Acceptable. No adverse effect.** (M. Silva, 5/5/97).

DNA DAMAGE

** 020 149230 "RH-70,345: Micronucleus Assay in CD-1 Mouse Bone Marrow Cells", (Sames, J.L. and Elia, M.C., Rohm and Haas, Spring House, PA; Protocol #: 94P-016; 11/29/94). Halofenozide technical (91.7% pure) was tested in a micronucleus assay using bone marrow cells from CD-1 mice (5/sex/dose/time point) after administration of a single oral (gavage) dose at 0 (corn oil), 141, 704 or 1408 mg/kg. Animals were terminated at 24 or 48 hours. Positive control animals were terminated at 24 hours. Bone marrow slides were prepared and the frequency of micronucleated polychromatic erythrocytes was measured as an indicator of cytogenetic damage. In addition poly- chromatic/normochromatic ratio was measured to evaluate cytotoxicity. Mice at $\geq$ 704 mg/kg showed signs of systemic toxicity up to 48 hours after treatment. Death occurred in one male and one female at 1408 mg/kg. There was no increased frequency of PCEs in bone marrow cells of either sex or at either time point. There was a statistically significant decrease in the PCE/NCE ratio, in addition to a dose response was observed in males at 48 hours (demonstrating toxicity). A similar effect was observed in females but was not statistically significant. **No adverse effect**. **Acceptable**. M. Silva, 5/5/97.

NEUROTOXICITY

** 015; 149220; "RH-70,345: Three-Month Dietary Toxicity/Neurotoxicity Study in Rats" (Anderson D.M. et al., Rohm and Haas Company, Toxicology Department, Spring House, PA, Report No. 93R-080, 3/31/95). 821/827. RH-70,345 Technical (Lot No. BM3033, purity=91.7%) was admixed to the feed at concentrations of 0, 1, 7.5, 75, or 750 ppm and fed to 15 Crl:CD®BR rats per sex per dose level continuous for a period of 3 months. One 1 ppm male animal was killed moribund during week 13 of the study. Statistically significant decreases in mean forelimb grip strength (in males and females) and in the number of rears in the open arena (in females), and

incidences of unkempt appearance in the open arena (in females) were observed during FOB assessments at 750 ppm. Statistically significant decreases in mean body weight, and red blood cell and hemoglobin levels and statistically significant increases in mean reticulocyte, methemoglobin, and glucose levels were observed in both males and females at 750 ppm. A statistically significant increase in mean relative liver weights was observed in both males and females at 750 ppm. Microscopic examination revealed hepatocellular hypertrophy, hemosiderin accumulation in hepatic Kupffer cells, increased pigment in spleen, and erythroid hyperplasia in bone marrow in both males and females at 750 ppm. **No adverse effects**. NOAEL (M)=52.7 mg/kg/day (750 ppm) and (F)=54.6 mg/kg/day (750 ppm). NOEL (M)=5.53 mg/kg/day (75 ppm) and (F)=5.88 mg/kg/day (75 ppm) (based on FOB assessments, decreased mean body weights, increased mean relative liver weights, clinical chemistry and histopathology). **Acceptable**. (Corlett, 7/22/97)

** 014; 149219; "RH-70,345: Acute Oral (Gavage) Neurotoxicity Study in Rats" (Morrison, R.D. et al., Rohm and Haas Company, Toxicology Department, Spring House, PA, Report No. HLR 93R-082, 11/22/94). 818. RH-70,345 (Lot No. BM3033, purity=91.7%), suspended in corn oil, was administered by gavage in a single dose at concentrations of 0, 200, 400, or 800 mg/kg to 10 Crl:CD®BR rats per sex per dose level. One male animal at 400 mg/kg and one male animal at 800 mg/kg died during the study (day 3). Treatment-related signs of red stained muzzle, scant feces, and diarrhea were observed at 400 and 800 mg/kg in males and at 200, 400, and 800 mg/kg in females. No treatment-related effects were seen in any FOB parameter in any test animal at any time during the study. Assessment of motor activity revealed a statistically significant increase in both mean total number of movements and mean total time spent in movement in females at 800 mg/kg. No compound-related gross or microscopic lesions were observed in the central or peripheral nervous system. **No adverse effects.** NOAEL (M/F)=800 mg/kg**.** NOEL (M)=200 mg/kg, (F)<200 mg/kg (based on clinical signs). **Acceptable**. (Corlett, 7/16/97)

SUBCHRONIC STUDIES

Oral/Neurotoxicity

** 016; 149221; "RH-70,345: Three-Month Dietary Study in Dogs" (Kaminski, E.J. et al., Rohm and Haas Company, Toxicology Department, Spring House, PA, Report No. 93R-081, 11/21/94). 821. RH-70,345 (Lot No. BM3033, purity=91.7%) was admixed to the feed at concentrations of 0, 30, 100, 300, or 1000 ppm and fed to 4 beagle dogs per sex per dose level daily for a period of 15 weeks. No animals died during the study. No treatment-related clinical signs were observed. Statistically significant decreases in mean red blood cell, hemoglobin, and hematocrit levels, statistically significant increases in mean platelet, reticulocyte, and methemoglobin levels, and incidences of Heinz bodies were observed in both males and females at 1000 ppm. Microscopic examination revealed slight to moderate hemosiderin in the cytoplasm of Kupffer cells of liver and in the cytoplasm of fixed macrophages in red pulp of spleen and minimal to moderate erythroid hyperplasia in bone marrow in both males and females at 300 and 1000 ppm. **No adverse effects**. NOEL (M)=3.7 mg/kg/day (100 ppm) and (F)=4.0 mg/kg/day (100 ppm) (based on histopathology-slight to moderate hemosiderin in the cytoplasm of Kupffer cells of liver and in the cytoplasm of fixed macrophages in red pulp of spleen and minimal to moderate erythroid hyperplasia in bone marrow). **Acceptable**. (Corlett, 6/30/97)

Dermal

** 017; 149222; "RH-70,345: Thirteen Week Dermal Toxicity Study in Rats" (Craig, L.P. et al.,

Rohm and Haas Company, Toxicology Department, Spring House, PA, Report No. 94R-018, 2/1/95). 823. RH-70,345 (Lot No. BM3033, purity=91.7%), moistened with tap water, was applied to the shaved skin of 10 Crl:CD®BR rats per sex per dose level at concentrations of 0, 40, 200, or 1000 mg/kg for 6 hours per day 5 days per week for 13 weeks using an occlusive wrap. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. Statistically significant decreases in mean red blood cell, hemoglobin, and hematocrit levels and statistically significant increases in mean methemoglobin levels in both males and females at 1000 mg/kg were observed. A statistically significant and dose-related increase in mean relative liver weights was observed in both males and females at 200 and 1000 mg/kg. Microscopic examination revealed increased pigment (hemosiderin) in the liver (Kupffer cells) and spleen in males (200 and 1000 mg/kg) and females (1000 mg/kg) and centrilobular to midzonal hepatocellular hypertrophy in both males and females at 200 and 1000 mg/kg. **No adverse effects**. NOEL (systemic, M/F)=40 mg/kg/day (based on increased mean relative liver weights). NOEL (dermal, M/F)=1000 mg/kg (no treatment-related skin effects). **Acceptable.** (Corlett, 7/2/97)