

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH**

**SUMMARY OF TOXICOLOGY DATA
2-BROMO-4-HYDROXY-ACETOPHENONE**

Chemical Code # 969, Tolerance # 51573
SB 950 # 540

Original date: October 10, 2002, revised April 11, 2003

I. DATA GAP STATUS

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|-------------------------|--|
| Chronic toxicity, rat: | Data Gap, no study on file. |
| Subchronic, rat oral: | No data gap, no adverse effect |
| Subchronic, rat dermal: | No data gap, no adverse effect (other than dermal) |
| 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: | No data Gap, no adverse effect. |
| Gene mutation: | No data gap, no adverse effect |
| Chromosome effects: | No data gap, no adverse effect |
| DNA damage: | No data gap, no adverse effect |
| Neurotoxicity: | Not required at this time. |

Toxicology one-liners are attached.

All record numbers through 203062 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T030411

Original: J. Kishiyama and Gee, October 10, 2002, revised by Gee, April 11, 2003

BHAP is a non-food use antimicrobial. The US EPA issued a "Reregistration Eligibility Decision (RED)" in February of 1995.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

CHRONIC TOXICITY, RAT

No study on file.

Subchronic:

** 51573 - 006 132360 Tompkins, E. C. "A 90-Day Oral Toxicity Study of BHAP in Rats with Four Week Recovery Period." (WIL Research Laboratories, Inc., WIL-94050, June 30, 1994.) BHAP, purity 31.9%, batch 2365, was administered via gavage at doses of 0 (corn oil), 6, 30, or 60 mg/kg/day (not adjusted for purity) to 10 CrI:CD®BR rats/sex/group with ten additional control and high dose animals/sex for a 4-week recovery period. BHAP at the high dose of 60 mg/kg resulted in mortality and, therefore, the dose was lowered to 45 mg/kg/day at week seven. Suppurative inflammation of the trachea in some mid and high dose males and females was considered partially responsible for the high mortality. Clinical signs of gasping, labored breathing and, especially, rales were observed in the mid and high dose groups. Other clinical signs included decreased defecation, salivation, and nasal discharge. Body weight and food consumption for high dose males were lower although females were comparable to controls. Testes weights were decreased for mid and high dose males at week 13 but not for the high dose recovery group at week 17. With a limited number of survivors at week 17 for the high dose, the symptomatic effects on the trachea were no longer found. There were no treatment-related effects on hematology, clinical chemistry, urinalysis or ophthalmology. NOEL = 6 mg/kg/day (clinical signs). Evaluated as unacceptable, upgradeable (clarification of the test article content and whether it was technical grade). (Kishiyama and Gee, 10/9/02). Document 51573-014, letter from Carl F. Watson, Buckman, dated January 15, 2003, no record number, contains a statement that the test material was technical grade 1448-367, with a nominal purity of 33%. Confirmation of the identity of the test article upgrades the study to ACCEPTABLE status. No worksheet. (Gee, 2/6/03)

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

** 51573 - 003 114096 Rodwell, D. E. "A Teratology Study in Rats with BHAP." (WIL Research Laboratories, Inc., Project No.: WIL-94018, March 27, 1987.) BHAP (purity 31.9%, batch 1785) was administered via gavage at doses of 0 (corn oil/1% Tween® 80), 10, 30, or 100 mg/kg/day to 25 bred Sprague-Dawley COBS® CD® rats/group during gestation days 6 through 15. Statistically significantly reduced food consumption was recorded for high-dose group days 12 through 20 and for the mid-dose group, days 12 - 16 (19 g/animal/day versus 22 for controls). Some high dose animals exhibited respiratory rales both pre-dose and post-dose and a few had yellow and/or clear material around the mouth. Maternal NOEL = 30 mg/kg (clinical signs, lower food consumption) There was no evidence of developmental toxicity. Developmental NOEL = 100 mg/kg. Unacceptable. Upgradeable (rationale for dose selection with range-finding study (WIL-94017), justification for the test article at approximately 30%). (Kishiyama and Gee, 10/9/02) The range -finding study was submitted and reviewed. See record 203062 below. This upgrades the study to ACCEPTABLE status. The range-finding study also clarifies the test article. NOTE: The doses given were not corrected for purity so that the actual doses of BHAP were approximately 30% of the nominal dose. (Gee, 4/10/03)

51573 - 018 203062 Rodwell, D. E. " A range-finding teratology study in rats with BHAP." (WIL Research Laboratories, Project No. WIL-94017, 3/27/87) Mated female Crl:CD®BR rats, 5/group, were given doses of BHAP (lot 1785, 31.9%) of 0 (vehicle), 5, 15, 35, 75 or 150 mg/kg/day by oral gavage gestation days 6 through 15. Doses were not corrected for purity. There were two deaths at 75 mg/kg/day and one at 150 mg/kg/day. Clinical signs were related primarily to those dams which died. There were no effects on fetal parameters for the limited set that were examined. No fetal weights were recorded and fetuses were not examined for malformations. Body weight of dams was not affected. Supplemental study for dose selection for the definitive study, record # 114096 in 51573 - 003. (Gee, 4/10/03)

TERATOLOGY, RABBIT

51573 - 0014 202553 Nemec, M. D. " A range-finding developmental toxicity study of 2-bromo-4'-hydroxyacetophenone in rabbits." (WIL Research Laboratories, Inc., WIL-94035, August 20, 1993) BHAP (total listed 46%, 31.4% pure, dosing solutions not corrected for purity) was given to 6 New Zealand White rabbits per group at doses of 0 (corn oil), 6.25, 12.5, 25, 50 or 100 mg/kg/day, days 7 - 19 of gestation, by oral gavage. At day 29, does were sacrificed and fetuses were given an external exam only. There were no deaths. Clinical signs of rales and/or labored respiration were noted at 50 and especially at 100 mg/kg/day. Two of 4 pregnant does at 100 mg/kg/day had only early resorptions. Body weight loss occurred at 100 mg/kg. Food consumption was severely reduced during dosing at 100 mg/kg and moderately reduced at 50 mg/kg/day. There were no external findings for fetuses at any dose and body weights were comparable. Maternal NOEL = 25 mg/kg, developmental NOEL = 100 mg/kg. Supplementary range-finding study. (Gee, 2/6/03).

** 51573 - 017 203061 Nemec, M. D. " A developmental toxicity study of 2-bromo-4'-hydroxyacetophenone in rabbits." (WIL Laboratories, WIL-94036, July 1, 1994) BHAP (batch 2365, 31.4%) was used to treat New Zealand White rabbits (20/group) at doses of 0 (corn oil), 10,

30 or 60 mg/kg/day by oral gavage, days 7 - 19 of gestation. Dose preparations were not corrected for purity so that the actual doses of BHAP were approximately 31% of the nominal doses above. There were 18, 14, 15 and 15 does with viable fetuses at necropsy after one doe aborted in each of the 10 and 30 mg/kg/day groups. One female at 10 and 30 and 3 at 60 mg/kg/day died. One of the three at 60 died from intubation error and the other two were attributed to treatment. At 60 mg/kg/day and to a lesser degree at 30 mg/kg/day, body weight, weight gain and food consumption were lower than in the control and 10 mg/kg/day groups. There were no treatment-related effects on fetal parameters including resorptions, fetal weight and malformations/variations. Maternal NOEL = 10 mg/kg/day; developmental NOEL = 60 mg/kg/day. No adverse effects. ACCEPTABLE. (Gee, 4/10/03)

GENE MUTATION

51573 - 001 064023 Sernau, R. C., Study Director. "CHO/HGPRT Forward Mutation Assay: BHAP: Final Report." (Hazleton Biotechnologies Corp., HBC Project No: 197-185, October 8, 1985.) BHAP, purity assumed 100%, specific gravity = 1.25, was evaluated for potential mutagenicity at concentrations of 0, 0.5, 1.0, 2.5, 5.0, and 7.5 µg/ml without activation and at 0, 2.5, 5.0, 7.5, 10 and 25 µg/ml in the presence of metabolic activation (source not stated). There were duplicate cultures in the single trial. Exposure time to Chinese hamster ovary cells was for 5 hours, followed by an eight-day expression period before plating for 6-thioguanine resistance (5 plates per initial culture). BHAP exposure did not increase mutation frequency compared with negative controls. Positive controls were functional. UNACCEPTABLE, not upgradeable (single trial). Also, the test article was not defined, other than as a black liquid. (Kishiyama and Gee, 9/24/02).

** 51573 - 001 064026 Cavagnaro, J., Study Director. "Mutagenicity Evaluation of BHAP Lot # GLB62985 in the Ames Salmonella/Microsome Plate Assay." (Hazleton Biotechnologies Corp., HB Project No.: 20988, December 1985.) BHAP was evaluated for potential mutagenicity at concentrations of 0 (DMSO), 0.12, 0.37, 1.1, 3.3, and 10 µg/plate with and without rat liver metabolic activation using Salmonella strains TA98, TA100, TA1535, TA1537 and TA1538. There were triplicate plates per concentration with a single trial. Test article exposure time was forty-eight hours. BHAP treatment with and without S9 Mix did not increase the number of revertants relative to the solvent control. Positive controls were functional. ACCEPTABLE. (Kishiyama and Gee, 10/8/02).

CHROMOSOME EFFECTS

** 51573 - 001 064025 Ivett, J. L., Study Director. "Clastogenic Evaluation of BHAP Lot No. GLB62985 in the In Vivo Mouse Micronucleus Assay." (Hazleton Biotechnologies Corp., HB Project No: 20996, February 1986.) BHAP, purity assumed 100% (density = 1.30 g/ml), was evaluated for the potential to induce micronuclei in bone marrow polychromatic erythrocytes in ICR strain mice, 5/sex/group, with a single (IP) injection at doses of 0 (corn oil), 70, 233 or 700 mg/kg. Animals were sacrificed at 24, 48 or 72 hours after treatment. BHAP treatment under study conditions did not significantly increase micronuclei in bone marrow erythrocytes. ACCEPTABLE. (Kishiyama and Gee, 10/7/02)

DNA DAMAGE

** 51573 - 001, 015 064024, 202554 Sernau, R. C., Study Director. "Unscheduled DNA Synthesis Rat Hepatocyte Assay with BHAP." (Hazleton Biotechnologies Corp., HBC Project No: 197-186, December 5, 1985.) BHAP, purity assumed 100%, lot GLB62985, was evaluated for induction of unscheduled DNA synthesis in male rat liver hepatocytes at concentrations of 0 (DMSO) 0.1, 0.25, 0.5, 1, and 2 µg/ml in duplicate cultures by autoradiography. Test article exposure time was "overnight" (actual time was not specified). BHAP treatment did not significantly increase nuclear grain counts. Evaluated as unacceptable but upgradeable (no individual data including cytoplasmic counts, nuclear counts and actual exposure time). (Kishiyama and Gee, 10/7/02). Document 51573-015, record 202554 was submitted. It contained a statement that exposure was 19 hours and also contained the individual cell data as requested, allowing for independent evaluation. The amendment was submitted through Covance Laboratories, Inc. The study was upgraded to ACCEPTABLE status with no adverse effect. No additional worksheet. (Gee, 2/7/03)

NEUROTOXICITY

Not required at this time.

OTHERS:

** 51573 016 202555 Adam, G. P., Study Director. "21-Day repeated dose dermal toxicity study in rabbits with BHAP." (WIL Laboratories, WIL-94021, January 16, 1987) BHAP (batch 1785, listed as 46.03%) was applied to the clipped skin the 5 New Zealand White rabbit per sex at doses of 0 (deionized water), 20, 100 or 500 mg/kg/day, 6 hours per day, 5 days per week for 3 weeks (15 total applications). Test article was applied neat and the volume applied per dose based on a specific gravity of 1.3 g/ml; volumes were 0.015, 0.077 and 0.385 ml/kg BHAP with increasing dose. Application sites were occluded during exposure and wiped at the end of the 6 hours. Hematology and clinical chemistry parameters were evaluated with no treatment-related findings. Organ weights, body weights and food consumption, although showing some variation, were not statistically different from controls. Clinical and histological findings were limited to the treated skin with findings of erythema, edema, fissuring, necrosis, desquamation, subcutaneous hemorrhaging and scabbing seen at all treatments, although the incidence and severity of some findings increased with dose. Systemic NOEL = 500 mg/kg/day; local NOEL < 20 mg/kg/day. ACCEPTABLE, although no ophthalmology was included in the protocol at that time. No adverse systemic effect. (Gee, 2/7/03).