

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
HEXAHYDRO-1, 3, 5-TRIS- (2-HYDROXYETHYL)-S-TRIAZINE

Chemical Code # 001171, Tolerance # 50300
SB 950 # 697
3/30/01, revised 8/9/02

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study submitted.
Subchronic, rat	No data gap, acceptable subchronic studies.
Chronic toxicity, dog:	Data gap, no study submitted.
Oncogenicity, rat:	Data gap, no study submitted.
Oncogenicity, mouse:	Data gap, no study submitted.
Reproduction, rat:	Data gap, no study submitted.
Teratology, rat:	No data gap, no adverse effects.
Teratology, rabbit:	Data gap, no study submitted.
Gene mutation:	No data gap, possible adverse effects
Chromosome effects:	No data gap, no adverse effects
DNA damage:	Data gap, study inadequate, possible adverse effect.
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 183790 and volumes through 023 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T020809

Original: Kishiyama and Gee, 3/30/01, revised 8/9/02 by Gee.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

No Study Submitted

CHRONIC TOXICITY, RAT

Subchronic:

** 009 117038 Hill, R. E. and A. J. Newman. "Triazine 13 Week Oral (Gavage) Toxicity Study in the Rat." (Toxicol Laboratories Limited, LEF/3/89, April 25, 1990.) Triazine [hexahydro-1, 3, 5-tris-(2-hydroxyethyl)-s-triazine], 78.5% purity, was administered via gavage at doses of 0 (distilled water), 10, 50, 100, or 250 mg/kg/day to 10 CrI: CD(SD) BR (VAF plus) rats/sex/group for 13 weeks. Noisy respiration occurred in 2/10 high-dose females with 4/10 deaths (not the same animals) from unexplained causes although there was evidence of triazine in the lungs. Stomach effects (erosion and lymphocytic infiltration) were seen at 100 and 500 mg/kg. There were other statistically significant findings but they were of doubtful toxicological significance. NOEL = 10 mg/kg for males (decrease in the incidence of margination of hepatocyte cytoplasm at 50 mg/kg (0/10 versus 7/10 in controls – considered as possibly due to non-specific stress by the authors) and NOEL = 50 mg/kg for females (stomach effects, possibly due to the corrosive property of triazine). No adverse effects were identified. ACCEPTABLE. (Kishiyama and Gee, 3/29/01).

** 50300 - 010, 023 117039, 183790 Hill, R. E., and A. J. Newman. "Triazine 13 Week Dermal Toxicity Study in the Rat". (Toxicol Laboratories Limited, LEF/4/89, April 26, 1990.) Triazine [hexahydro-1, 3, 5-tris (2-hydroxyethyl)-s-triazine], purity 78.5%, was administered dermally at doses of 0 (water), 5, 50 or 250 mg/kg/day to 10 Sprague-Dawley rats/sex/group. The doses of 5 and 50 mg/kg/day were applied in 2 ml/kg, diluted in water. The high dose, 250 mg/kg, was applied neat at 0.216 ml/kg. Exposure time was 6 hours/day, 5 days/week for 13 weeks. Because triazine was considered a skin irritant, applications were made to four quadrants of the application area on sequential days. The sizes of the application areas were not identified. Erythema at the application sites was seen with increasing incidence and severity at 50 and 250 mg/kg/day. No effects were seen in males at the low dose but 2/10 females showed very slight erythema for 2 days and 7 days. Edema was seen on "occasion" and "isolated" at the high and mid doses, both sexes. Dermal NOEL = 5 mg/kg/day (skin irritation at the site of application); Systemic NOEL >250 mg/kg/day (no effects). Evaluated as unacceptable but upgradeable (information on the application sites). (Kishiyama and Gee, 3/30/01). Document 50300 - 023, record 183790, contains two letters addressing the application site. With this information, the study is considered ACCEPTABLE. (Gee, 8/9/02)

015 131022: Same study as 010 117039.

CHRONIC TOXICITY, DOG

No Study Submitted

ONCOGENICITY, RAT

006 068862 “A study of biocides for selection of candidates for carcinogen bioassay.” (Johnson, O. H. et al., published in: *J. Environ. Sci. Health, A19* (1), 1 – 25 (1984), SRI International) Hexahydro-1,3,5-(tris(2-hydroxyethyl)triazine was one of eight chemicals from an initial list of 295 that were considered for evaluation, based on possible carcinogenic activity and human exposure. In the case of this test material, the suspicion of carcinogenicity was “unknown” but was nominated based on exposure as a biocide in cutting oil emulsions. It was rejected as a candidate in the final decision. No worksheet. (Gee, 3/27/01)

No Study Submitted

ONCOGENICITY, MOUSE

No Study Submitted

REPRODUCTION, RAT

No Study Submitted

TERATOLOGY, RAT

** 011 117040 Ridgway, P. “Triazine Rat Teratology Study”. (Toxicol Laboratories Limited, LEF/8/89, June 16, 1989.) Triazine [hexahydro-1, 3, 5-tris-(2-hydroxyethyl)-s-triazine], 78.5%, was administered via gavage at doses of 0 (distilled water), 250, 500 and 750 mg/kg/day to 24 Sprague-Dawley (OFA-SD (IOPS-Caw)) rats/group, days 6 through 15 of gestation. Food consumption and body weight gain were reduced at 750 mg/kg/day. The incidences of post-dosing salivation and ulceration of the stomach were increased for high dose females. Rales and wheezing were seen on 2 and 1 occasion at 500 mg/kg. MATERNAL NOEL = 250 mg/kg/day (clinical signs). No evidence of developmental toxicity was reported. DEVELOPMENTAL NOEL = >750 mg/kg/day. ACCEPTABLE. (Kishiyama and Gee, 4/2/01).

TERATOLOGY, RABBIT

No Study Submitted

GENE MUTATION

006 068892 Johnson, I. “Ames Test (O.E.C.D.) Product Glokill 77”. (SafePharm Laboratories Ltd, England, Report No. 1047/8/J, September 11, 1984.) Glokill 77 (clear liquid, no purity stated) at concentrations of 0 (deionized water), 0.16, 0.8, 4, 20, and 100 µg per plate, with and without metabolic activation (S9 Mix), was tested with *Salmonella typhimurium* strains TA 1535, TA 1537, TA1538, TA 98, and TA 100 for mutagenic activity. Exposure time was 48 hours at 37° C. There were triplicate plates per concentration with repeat a repeat trial. Positive controls were functional. Revertant increases were observed with *Salmonella typhimurium* strains TA 1538 (+S9 and –S9) and

with TA 98 (+S9). UNACCEPTABLE. Upgradeable (characterization of test article). (Kishiyama and Gee, 3/28/01).

** 012 117071 Asquith, J. C. "Triazine Joint Venture Bacterial Reverse Mutation Assay - Triazine". (Toxicol Laboratories Limited, Study No.: M/Ames/10658, February 8, 1989.) Triazine [hexahydro-1, 3, 5-tris(hydroxyethyl)-s-triazine], purity 78.5%, was evaluated for mutagenicity at concentrations of 0, 0.32, 1.6, 8, 40, and 200 µg/plate, with and without metabolic activation by S9 Mix, using *Salmonella typhimurium* strains TA 1535, TA 1537, TA1538, TA98, and TA100. Exposure time was 72 hours by plate incorporation. There was no increase in the number of revertants. ACCEPTABLE. (Kishiyama and Gee, 4/2/01).

CHROMOSOME EFFECTS

006 068893 Urwin, C., J. C. Richardson, and A. K. Palmer. "An Evaluation of the Mutagenicity of the Cutting Oil Preservative Grotan BK." (Huntingdon Research Centre (UK), published in: *Mutation Research*, 40: 43 - 46 (1976)) Grotan BK, purity not stated, was tested at doses of 0 (4% cutting oil/water emulsion), 7.5, 30, 120, or 480 mg/kg/day given twice (24 hours apart) by the oral, subcutaneous, or dermal route to 5 CFHB (Wistar) rats/sex/group. Animals were sacrificed 6 hours after the second dosing and bone marrow smears prepared. A total of 2000 polychromatic erythrocytes for each animal were scored for micronuclei. No evidence of micronuclei formation was reported. The positive control, benzidine, was effective by the subcutaneous and dermal routes. UNACCEPTABLE (report lacks many details of methods and results, single sacrifice time.) Not upgradeable. (Kishiyama and Gee, 3/28/01.)

** 012 117041 Asquith, J. C. "Triazine Joint Venture Mouse Micronucleus Test". (Toxicol Laboratories Limited, Study No.: M/MMN/10659, February 3, 1989.) Triazine [hexahydro-1, 3, 5-tris(hydroxyethyl)-s-triazine], purity 78.5%, was administered as a single gavage at doses of 0 (0.9% saline), 200, 400, or 800 mg/kg to 15 CD-1 mice/sex/group. Scheduled sacrifices were at 24, 48 or 72 hours post-dosing, 5/sex/dose. Marrow from both femurs of each mouse was evaluated for micronuclei in polychromatic erythrocytes, scoring approximately 1000 PCEs per animal from two slides. The positive control, cyclophosphamide, was functional at 24 hours. There was no significant change in PCE/NCE with dose. No dose related increase in MN-PCE was reported. No adverse effects. ACCPETABLE. (Kishiyama and Gee, 4/2/01).

DNA DAMAGE

012 117073 Curren, R. D. "Unscheduled DNA Synthesis in Rat Primary Hepatocytes". (Microbiological Associates, Inc., Laboratory Study No.: T8102.380, July 20, 1988.) Hexahydro-1,3,5-tris-(2-hydroxyethyl)-s-triazine, purity not stated, was evaluated for its ability to induce unscheduled DNA synthesis in primary rat hepatocytes at 7 dose levels ranging from 0.001 to 1.0 µl/ml. Three replicates per treatment concentration were scored with 50 cells per culture. Cytotoxicity was determined by lactic acid dehydrogenase release. The test article was too toxic at dosages of 0.3 and 1.0 µl/ml for analysis. Triazine (0.1 µl/ml) significantly increased the number of net grains per nucleus (11.4 versus -2.1 in controls) and the percent of cells with 5 or more net nuclear grains was 92% versus 2 -3 % in the controls. The percent of cells with 5 or more grain counts at 0.03 µl/ml (next lower concentration) was 4% and the net grain count was 0.2. Because of the lack of a dose response, the results were considered equivocal. Individual cell data were not included. UNACCEPTABLE. Upgradeable (test article purity). (Kishiyama and Gee, 4/2/01)

006 073111: Same study as 012 117073.

NEUROTOXICITY

Not required at this time.