

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
CHLOROPHACINONE

Chemical Code #001625, Tolerance # 07173
SB 950 # 573
July 2, 2002

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study submitted Subchronic study submitted, inadequate with no adverse effects (other than related to anticoagulant activity)
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, possible 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:	Data gap, inadequate study, no adverse effect indicated
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 135352 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T020702

Revised by: J. Kishiyama and Gee, July 2, 2002

Reregistration Eligibility Document (RED): Rodenticide Cluster, July 1998, available from the US EPA web site, www.epa.gov/pesticides/reregistration/status.htm. Not on file at DPR. [See CC 2049 file in Medical Toxicology for a partial copy.]

I. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

CHRONIC TOXICITY, RAT

No study submitted.

SubChronic:

50106 - 021 115347 Baron, R. L. (Study authors: C. Mally, G. Porret-Blanc and G. Lorgue). APhase 3 Reformat: 3 Month Toxicity Study on Rats by Oral Method@ (Lipha Centre de Recherches, France, LCR #84.05. LM91 RPP, original dated 12/18/84, reformatted March 10, 1990.) Chlorophacinone technical (purity not stated) was administered via gavage at concentrations of 0, 5 (terminated at 77 days), 10 and 20 µg/kg/day, at 0 and 40 µg/kg/day for 112-113 days and at 0, 80 or 160 µg/kg/day to 10 Sprague-Dawley rats/sex/group. Animals in dose groups 40 µg/kg/day and above had excessive and rapid mortality and signs characteristic of intoxication by an anticoagulant. Hemorrhage was frequent in various organs and found in almost all animals in 20 µg/kg and above. Coagulating time was increased for rats in dose groups 10 µg/kg/day and above (not measured at 5 µg/kg). Serum chemical changes varied between the sexes and dosages, but generally were elevated for the higher dose groups and suggestive of hepatic and renal disorders. Body weight gain and food consumption were lower and influenced by the decline in general health prior to death of affected animals. LOEL = 10 µg/kg, ENEL = 5 µg/kg, based on the minimal effects at 10 µg/kg. UNACCEPTABLE (rationale for initial dose selection of 0, 5, 10, and 20 µg/kg not discussed, low dose group terminated at 77 days without clinical chemistry, no ophthalmological examination, histopathology performed on too few animals/group, others). Not upgradeable. No adverse effects other than those associated with an anticoagulant. (Kishiyama and Gee, 6/26/02).

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, RAT

No study submitted.

ONCOGENICITY, MOUSE

No study submitted.

REPRODUCTION, RAT

No study submitted.

TERATOLOGY, RAT

** 50106 027 135251 Tyl, R. W., M. C. Marr and C. B. Myers. ADevelopmental Toxicity Evaluation of Chlorophacinone Administered by Gavage to CD7 (Sprague-Dawley) Rats.@ (Research Triangle Institute, RTI ID No. 65C-5724-01/02, July 21, 1994.) Chlorophacinone, purity of 100%, was administered by gavage at doses of 0, 12.5, 25, 50, or 100 µg/kg/day to 25 sperm-positive CD7 females/group during gestational days 6 through 15. Mortality was 72% (18/25) for the 100 µg/kg/day group. Pre- and postmortem observations indicated an anticoagulation mechanism mode of action for chlorophacinone at 100 µg/kg/day. Maternal NOEL = 50 µg/kg/day. The majority of visceral malformations were bilateral hydroureter and the upward trend was dose-related. The authors suggested that hydroureter in fetuses now appears to be more common in control CD7 rats.

The upward dose-related trend in **bilateral/unilateral hydroureter (malformation) and distended ureter (variation) with chlorophacinone appeared to be a possible adverse effect**. The litter incidence, however, was not significant by pairwise comparison (8/25, 10/24, 14/25, 14/24 and 5/7 for total ureter findings). Developmental NOEL = 12.5 µg/kg/day. In the range-finding study, using 2 - 5 dams per dose on day 16, there were no statistically or biologically significant differences in prothrombin or activated partial thromboplastin times, up to 50 µg/kg/day. ACCEPTABLE. (Kishiyama and Gee, 7/1/02).

TERATOLOGY, RABBIT

** 50106 - 028 135252 Tyl, R. W., M. C. Marr and C. B. Myers. A Developmental Toxicity Evaluation of Chlorophacinone Administered by Gavage to New Zealand White Rabbits.® (Research Triangle Institute, RTI ID No. 65C-5724-03/04, January 9, 1995.) Chlorophacinone, purity of 101%, was administered by gavage at doses of 0 (corn oil), 5, 10, 25, or 75 µg/kg/day to 16 mated females/group during gestational days 7 through 19. Mortality was 100% and 81% for dose groups 75 and 25 µg/kg/day, respectively. Clinical observations and necropsy findings indicated anticoagulant activity (external and internal hemorrhaging). Maternal NOEL = 10 µg/kg/day (mortality and clinical signs) and the developmental NOEL = 10 µg/kg/day (at 25 µg/kg/day, there were 2 surviving litters and, although there were no effects in these litters, the number was too low for a definitive evaluation). There were no treatment-related developmental findings. In the range-finding study with 3 does/dose at 0, 1, 2, 5, or 10 µg/kg, PT (11.6 sec versus 8.1 in controls) and APTT (53.0 sec versus 26.5 sec, significant by trend test) were slightly elevated at 10 µg/kg. ACCEPTABLE. (Kishiyama and Gee, 7/1/02)

GENE MUTATION

** 50106 - 020 115343 Weill, N. A Test to Evaluate the Induction of Genic Mutations in CHO Cells (HGPRT Locus): Chlorophacinone.® (Hazleton France, Laboratory Project ID 006301, July 9, 1990.) Chlorophacinone (batch CLOM 027, 98.58%) was evaluated for mutagenic potential at concentrations of 5×10^{-3} , 10^{-2} , 5×10^{-2} , 10^{-1} , 2×10^{-1} mg/ml (0.005, 0.01, 0.05, 0.1 and 0.2 mg/ml) with and without metabolic activation (S9 Mix) using CHO cells. There were two trials with a single culture per concentration. Exposure was for 4 hours followed by an expression period of 7 days. At the end of the expression time, 12 plates per concentration were made for mutation frequency using 6-thioguanine to select mutants. In trial 1, with S9, there was a statistically significant increase in mutant frequency at 0.2 mg/ml. This was not reproduced in trial 2. Also, the cloning efficiency after treatment indicated this concentration was excessively toxic. Results without activation were negative. Positive controls were functional. Overall, there was no consistent evidence of mutagenic activity with chlorophacinone under the conditions of the assay. ACCEPTABLE. (Kishiyama and Gee, June 27, 2002)

** 50106 - 020 115345 Betbeder-Matibet, A. A Research on the Mutagenic Potential of Chlorophacinone using the Ames Test.® (Lipha Bacteriology Laboratory, France, July 1981.) Chlorophacinone (99.8%) was tested by plate incorporation at concentrations of 0 (DMSO), 2, 10, 50, and 250 µg per plate, with or without metabolic activation (S9 Mix) using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100. The S9 was prepared with female Sprague-Dawley rats induced with phenobarbital and naphthoflavone rather than males and Aroclor 1254 (no rationale). There were triplicate plates per concentration, one trial. Positive controls were β-propiolactone, dantrolene or niridazole. Toxicity was seen at 250 µg/plate in all strains ± activation. Positive controls were functional. Chlorophacinone exposure with and without metabolic activation did not increase the number of revertants under the conditions of the assay. ACCEPTABLE. (Kishiyama and Gee, 6/28/02).

CHROMOSOME EFFECTS

** 50106 - 020 115344 Weill, N. A Test to Evaluate the Ability to Induce Chromosome Aberrations

in Human Lymphocytes (LYMP.): Chlorophacinone@ (Hazleton France, Laboratory Project ID 006327, July 9, 1990.) Chlorophacinone, purity 98.58% was tested at concentrations of 0 (DMSO), 5×10^{-2} , 10^{-1} , and 2×10^{-1} mg/ml [0.05, 0.1 and 0.2 mg/ml] with and without metabolic activation (S9 Mix) using human lymphocytes in whole blood for genotoxic potential. There were an additional trial with activation using 0.15 mg/ml. There was a single culture per concentration with two slides prepared for analysis of aberrations. Mitotic index was used as a measure of toxicity. Lymphocytes were incubated with the test article for 3 hours followed by an additional 22 hours plus two hours with colchicine before termination. The sex of the donor was not identified. No evidence of induction of chromosomal aberrations was reported in the presence of cytotoxicity under assay conditions. Positive controls were functional. ACCEPTABLE. (Kishiyama and Gee, 6/28/02).

DNA DAMAGE

50106 - 020 115346 Betbeder-Matibet, A. AResearch on the *In Vivo* Mutagenic Potential of Chlorophacinone using the Micronucleus Test.@ (Lipha Bacteriology Laboratory, France, July 1981.) Chlorophacinone was administered at doses of 0 (gum arabic), 22.5, 45 and 90 mg/kg via single gavage/day over a period of 2 days to 3 albino mice/sex/group with sacrifice at 6 hours after the second treatment. There was no evidence of toxicity and no evidence of an increase in micronucleated polychromatic erythrocytes chlorophacinone exposure. Normochromatic erythrocytes were not scored. UNACCEPTABLE. Not Ungradable (too few animals/sex/group; rationale for dose selection not reported and single sacrifice time of 6 hours after the second dosing). (Kishiyama and Gee, 6/28/02).

NEUROTOXICITY

Not required at this time.

OTHER

According to the US EPA RED, July 1998, there is a 21-day dermal toxicity study in rabbits that is not on file with the Department. The study was identified as: AHamada, N. (1992) 21-Day dermal study in rabbits with chlorophacinone: Final Report: Lab Project Number 2624-104, 105, 106. Unpublished study by Hazleton Washington, 677 p.@ Page 24 of the RED summarizes the study and states the NOEL to be 80 $\mu\text{g}/\text{kg}/\text{day}$ based on increased prothrombin times at the next higher dose of 400 $\mu\text{g}/\text{kg}/\text{day}$ (doses in terms of chlorophacinone). At 2000 $\mu\text{g}/\text{kg}/\text{day}$, 4/5 males and 1/5 females died with Awidespread@internal hemorrhage). The material used was 0.2% chlorophacinone in a formulated product, applied 6 hours/day, 5 days per week, 5 rabbits/sex/dose. (Gee, 7/2/02)

There is an older dermal study with rabbits in 50105-002, record 950386, in which Rozol (0.2% tracking powder) was applied to male albino rabbits for 6 hours per treatment, 5 days per week for 3 weeks at doses of 10, 100 or 500 mg/kg/day. Approximately 15 to 20% of the body surface was covered. There was no mortality at 10 mg/kg/day. All animals died at the other two doses. From a notation it appears that the doses were in terms of chlorophacinone. Report consists of 3 pages. No worksheet. (Gee, 7/2/02)