

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
DENATONIUM SACCHARIDE

Chemical Code # 003981, Tolerance # 52048
March 30, 2000

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, inadequate study, no adverse effect indicated
Chronic toxicity, monkey:	Data gap, inadequate study, no adverse effect indicated
Chronic toxicity, dog:	Data gap, no study on file, however see "monkey", above
Oncogenicity, rat:	Data gap, inadequate study, no adverse effect indicated
Oncogenicity, mouse:	Data gap, no study on file
Reproduction, rat:	Data gap, no study on file
Teratology, rat:	Data gap, no study on file
Teratology, rabbit:	Data gap, no study on file
Gene mutation:	Data gap, no study on file
Chromosome effects:	Data gap, no study on file
DNA damage:	Data gap, no study on file
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

All record numbers through 170361 (Document No. 52048-006) were examined. This includes all studies on file with DPR as of 3/27/00.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T20000330.doc

Prepared by H. Green and C. Aldous, 3/30/00.

NOTE: Existing studies utilize the benzoate salt (Chemical Code 2229). The active registration is for the saccharide.

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

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

The 1978 IRDC study below does not indicate adverse health effects. The lack of dosing material characterization, coupled with lack of evidence of compound toxicity, limit the value of the information about the potential toxicity of this compound. Acknowledging these deficiencies, the lack of evidence of treatment effects at dose levels up to 16 mg/kg/day is potentially important. Considering that oral consumption of significant amounts of this material is likely to be extremely unlikely due to its extreme bitterness, the data in Record No. 170360 give no reason for concern about its potential chronic toxicity. Aldous, 3/30/00.

52048-005 170360 E. I. Goldenthal *et al.*, IRDC study prepared for HUD. "Two Year Oral Toxicity Study in Rats", 11/22/78. Record # 52048-004 170358 is a week-78 interim report for this study. Sixty-five Charles River CD rats per sex per group received denatonium benzoate by gavage at 0, 1.6, 8.0, and 16.0 mg/kg/day for 24 months, with interim necropsies of 5 per sex at 3, 12, and 18 months. This study pre-dated many of the current guidelines, and thus many deficiencies were noted in design and conduct, some of which cannot be corrected (no analysis of dosing material, no quality assurance program, no evidence that the treatments were in a toxic range). No definitive treatment effects were noted, hence the apparent NOEL = 16 mg/kg/day. The study is not acceptable, and not upgradeable. No adverse effect is indicated. (H. Green and C. Aldous, 3/30/00).

CHRONIC TOXICITY, RAT

(See Combined, rat, above)

CHRONIC TOXICITY, MONKEY

52048-006 170361, "One Year Oral Toxicity Study in Monkeys", (E. I. Goldenthal, *et al.*, IRDC, Mattawan, MI., 2 March 1977). Eight cynomolgus monkeys (*Macaca fascicularis*) per sex per group received denatonium benzoate by gavage at 0 (distilled water), 1.6, 8.0, or 16.0 mg/kg/day for up to 1 year. Typically 4/sex/group were maintained for the full year: interim sacrifices of 2/sex/group were held at weeks 14 and 27 where survival permitted. The most extensively reported findings in this record are the EKG's, that comprise about 400 pages of this record. There were no definitive treatment effects, although premature deaths (other than due to injury or one case of pneumonia) were limited to the higher two dose groups. Apparent NOEL = 1.6 mg/kg/day, based on mortalities in 8 and 16 mg/kg/day groups (2/17 and 3/16, respectively), for which there were no associated clinical signs. These deaths were considered by investigators to be possibly treatment-related, however the absence apparent target organ toxicity at these dose levels tested suggests that the latter deaths were likely to

have been incidental. Indications of treatment effects on survival are **not** sufficient to designate findings as "possible adverse effects". **Unacceptable, not upgradeable** (major deficiencies included lack of dosing material analysis, lack of a clear dose-response, and the unexplained presence of five mortalities with no associated clinical signs nor other evidences of toxicity. (H. Green, and C. Aldous, 3/30/00).

CHRONIC TOXICITY, DOG

No study on file (however see "monkey", above)

ONCOGENICITY, RAT

No study on file (however see "combined, rat", above)

ONCOGENICITY, MOUSE

No study on file

REPRODUCTION, RAT

No study on file

TERATOLOGY, RAT

No study on file

TERATOLOGY, RABBIT

No study on file

GENE MUTATION

No study on file

CHROMOSOME EFFECTS

No study on file

DNA DAMAGE

No study on file

ACUTE STUDIES

Acute Studies on Technical Active Ingredient

**52048-003 170357, "Acute Oral Toxicity Studies in Rats and Rabbits" (Section on Acute Oral Toxicity (LD₅₀) in Male and Female Albino Rats) (R. G. Geil and W. P. Dean, IRDC, Mattawan, MI., 29 January 1976). Each of five Charles River CD rats per sex per group received a single gavage dose of denatonium benzoate at 127.1, 201.7, 320.2, 508.4, 807.0, or 1281.0 mg/kg followed by a 14 day observation period. LD₅₀ Males = 640 mg/kg. LD₅₀ Females = 584 mg/kg (Toxicity Category III). Common symptoms observed at dose levels up to 320 mg/kg were diarrhea, with occasional "decreased activity". Higher doses such as 508 mg/kg additionally produced common symptoms of salivation, ataxia, tremors, and decreased respiratory rate. Most of these signs occurred during the first

5 hours after dosing (pp. 5-6). Highly lethal dose levels (807 mg/kg and above) often killed within 15 minutes. Acceptable. No adverse effects. (H. Green and C. Aldous 3/23/00).

52048-003 170357, “Acute Oral Toxicity Studies in Rats and Rabbits” (Section on Acute Oral Toxicity (LD₅₀) in Neonatal Albino Rats), (R. G. Geil and W. P. Dean, IRDC, Mattawan, MI. 1/29/76). Ten Charles River CD neonatal rats per group, “undifferentiated as to sex”, received single doses of denatonium benzoate by gavage at 0, 7.9, 12.5, 19.8, 31.5, 50.0, 79.4, 125.0, or 315.0 mg/kg, followed by a 14-day observation period. Oral LD₅₀ = 23 mg/kg. There were no clinical signs among pups dosed up to 12.5 mg/kg. At doses near to the LD₅₀, non-specific signs such as cyanosis and hypothermia were occasionally observed. All pups necropsied from groups dosed above the LD₅₀ had “milk curd in stomach”, suggesting that death may have resulted from disturbance of function in the stomach or elsewhere in the alimentary tract. Most deaths occurred within the first 5 hours. Possible adverse effects (Category I for oral acute toxicity). **Unacceptable**. This is a supplemental study with significant design flaws (there was only one litter of 10 pups per dose level, no GLP or QA oversight, and relevance of treatment of neonates by gavage was not established). (H. Green and C. Aldous, 3/24/00).

52048-003 170357, “Acute Oral Toxicity Studies in Rats and Rabbits” (Section on Acute Oral Toxicity (LD₅₀) in Male and Female Albino Rabbits), (R. G. Geil and W. P. Dean, IRDC, Mattawan, MI., 1/29/76). Ten New Zealand White rabbits per sex per group received single doses of denatonium benzoate by gavage at 202, 320, 508, 807, and 1281 mg/kg followed by a 14-day observation period. Oral LD₅₀ Males = 508 mg/kg. Oral LD₅₀ Females = 640 mg/kg. Toxicity Category III. Supplementary study, useful data. No adverse effects indicated. (H. Green and C. Aldous, 3/24/00).

Studies on Ro-Pel Animal, Rodent and Bird Repellant

52048-002; 169421; 811; “Acute Oral Toxicity Limit Test”; (Gary Wnorowski; Product Safety Labs, East Brunswick, NJ; Laboratory Project Identification Number 3633; 5/23/95). Five rats/sex/dose were treated by gavage with 5,000 mg/kg of Ro-Pel Animal, Rodent and Bird Repellant (a.i.: 0.065%, a clear liquid). All test animals survived a 14 day observation period. Clinical observations revealed no abnormalities. Weight gain was normal. Gross necropsy findings at terminal sacrifice were normal. LD₅₀ > 5,000 mg/kg; Toxicity Category IV; **Study acceptable**. (Kahn, 7/1/99)

52048-002; 169422; 812; “Acute Dermal Toxicity Limit Test”; (Gary Wnorowski; Product Safety Labs, East Brunswick, NJ; Laboratory Project Identification Number 3636; 5/25/95). Five rats/sex/dose were exposed dermally for 24 hours to 5,000 mg/kg of Ro-Pel Animal, Rodent and Bird Repellant (a.i.: 0.065%, a clear liquid). All test animals survived the 24 hour exposure period and the 14 day post-dose observation period. Clinical observations revealed no abnormalities. Weight gain was normal. Gross necropsy findings at terminal sacrifice were normal. LD₅₀ > 5,000 mg/kg; Toxicity Category IV; **Study acceptable**. (Kahn, 7/1/99)

52048-002; 169423; 813; “Acute Inhalation Toxicity Limit Test”; (Gary Wnorowski; Product Safety Labs, East Brunswick, NJ; Laboratory Project Identification Number 3638; 5/25/95). Five rats/sex/dose were treated by inhalation for 4 hours (whole body) with 2.52 ± 0.14 mg/l [Average Gravimetric Value (GSD)] and 71.56 mg/l (Nominal Value) of Ro-Pel Animal, Rodent and Bird Repellant (a.i.: 0.065%, clear liquid). The MMAD was estimated to be 4.1 microns based on analysis of particle size distribution as measured with an Anderson Cascade Impactor. All test animals survived the 14 day observation period and gained body weight. Clinical observations revealed irregular

respiration, hunched posture and hypoactivity. Necropsy findings were unremarkable. LC50 > 2.52 mg/l (Gravimetric Value); Toxicity Category IV; **Study acceptable.** (Kahn, 7/7/99)

52048-002; 169424; 814; "Primary Eye Irritation"; (Gary Wnorowski; Product Safety Labs, East Brunswick, NJ; Laboratory Project Identification Number 3634; 5/23/95). The right eye of six rabbits was treated with 0.1 ml/eye of Ro-Pel Animal, Rodent and Bird Repellant (a.i.: 0.065%, a clear liquid). All animals survived a three day observation period. At Day 1 post-dose, Grade 1 conjunctival irritation was observed in three of six eyes. At Day 2 and 3 post-dose, no eye irritation was observed. Toxicity Category IV; **Study acceptable.** (Kahn, 7/7/99)

52048-002; 169425; 815; "Primary Skin Irritation"; (Gary Wnorowski; Product Safety Labs, East Brunswick, NJ; Laboratory Project Identification Number 3635; 5/23/95). 0.5 ml of Ro-Pel Animal, Rodent and Bird Repellant (a.i.: 0.065%, a clear liquid) was applied to the skin of 6 rabbits for an exposure period of 4 hours (semi-occluded). All animals survived a 3-day observation period. At Days 1-3 post patch removal, no dermal irritation. Toxicity Category IV; (Kahn, 7/7/99)