

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
DIDECYLDIMETHYLAMMONIUMCHLORIDE

Chemical Code # 1682, Tolerance # 50350
SB 950 # 475

July 24 1986

Revised 11/13/90, 5/19/95, 2/14/96

I. DATA GAP STATUS

| | |
|------------------------|---------------------------------|
| Combined, rat: | No data gap, no adverse effect. |
| Chronic toxicity, dog: | No data gap, no adverse effect. |
| Oncogenicity, mouse: | No data gap, no adverse effect. |
| Reproduction, rat: | No data gap, no adverse effect. |
| 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 143297, volume 50350-314 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T960214

Revised by H. Green & M. Silva, 5/19/95, M. Silva, 2/14/96

Didecyldimethylammoniumchloride has been designated by EPA as the representative chemical for toxicology studies for all dialkyl quaternaries. Other compounds in the group include: Dioctyl dimethyl ammonium chloride (SB# 444, DPN# 50356), Octyl decyl dimethyl ammonium chloride (SB# 455, DPN# 50348) and Octyl dodecyl dimethyl ammonium chloride (SB# 456, DPN# 50521). Medical Toxicology 1-liners for all the dialkyl quaternary studies are in the didecyldimethylammoniumchloride file.

According to the most recent "Rainbow Book" of USEPA, Spring, 1998, there are some additional active ingredients also considered as one case, including CC 1362 (Gee, 4/23/02)

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

** 171 098058, "Chronic Dietary Toxicity/Oncogenicity Study with Didecyldimethylammoniumchloride in Rats", (M.W. Gill, J.S. Chun & C.L. Wagner, Bushy Run Research Center, Export, PA., Report # 53-566, 6/27/91). Bardac 2280 (didecyl dimethyl ammonium chloride), 80.8% pure, was fed in diet to 60 Sprague-Dawley CD[®] rats/sex/group for 104 weeks at 0 (Ground Purina Certified Rodent Chow[®] # 5002), 300, 750, and 1500 ppm. Two control groups were included and treated as independent entities. Chronic NOEL = 750 ppm (Decreased bodyweight, bodyweight gain and food consumption was observed in both sexes at 1500 ppm. Increased incidence in mesenteric lymph node pathology (blood in sinuses, hemosiderosis and histiocytosis) occurred in both sexes at 1500 ppm. Bile duct hyperplasia occurred in females at 1500 ppm.) Treatment-related oncogenicity was not observed. **No adverse oncogenic effects were observed**, however, there were treatment-related changes in both sexes in the mesenteric lymph node (blood filled sinuses, hemosiderosis & hystiocytosis) and bile duct hyperplasia at 1500 ppm. **Acceptable**. (Green & Silva, 5/11/95).

CHRONIC TOXICITY, DOG

Subchronic Studies:

314 143296 "Short-Term Palatability Study of "Didecyl Dimethyl Ammonium Chloride," (G.E. Schulze, Hazleton Laboratories, Inc., Project ID #: HLA Study No. 2545-101, 4/24/90). DDAC technical (80.8% pure) was fed in diet to Beagle dogs (2/sex/dose) at 0, 30, 60 and 90 mg/kg/day for 21 days. NOEL = \geq 60 mg/kg (Body weights and food consumption were decreased at \geq 60 mg/kg. There was increased emesis, few or no feces and thinness (90 mg/kg only) primarily at \geq 60 mg/kg, and were considered to be related to DDAC.) **No adverse effect indicated**. Severe weight losses occurred, however, that was due to the lack of palatability of the DDAC in diet and not to compound toxicity. These data are supplemental. M. Silva, 1/24/96.

314 143297 "Subchronic Oral Toxicity Study of Didecyl Dimethyl Ammonium Chloride in Dogs," (M.R. Osheroff, Hazleton Laboratories America, Inc., Vienna, VA; HLA Study #: 2545-100, 4/24/90). DDAC technical (80.8% pure) was administered by gavage to Beagle dogs (2/sex/dose) at 0, 7.5 (increased to 60 mg/kg/day for weeks 5-8), 15, 30 and 60 mg/kg/day for 8 weeks. NOAEL = 7.5 mg/kg (Mortality increased at 60 mg/kg. At 7.5 mg/kg, animals showed soft, mucoid feces (weeks 1-4). At 15 mg/kg, animals showed increased emesis, soft feces and soft mucoid feces (single and divided dosing regimens). There was increased emesis, salivation, few or no feces, soft feces, soft mucoid feces, lacrimation and thin appearance at 60 mg/kg. Body weights and food consumption were decreased in a dose-related manner at all treatment levels during week 2 of the study. Animals switched from 7.5 mg/kg to 60 mg/kg showed decreased body weight gain and food consumption during weeks 5-8. There was a slight decrease in erythrocyte count, hemoglobin, hematocrit, mean cell volume and mean cell hemoglobin was observed in surviving dogs at 60 mg/kg/day week 8. Cholesterol was lower (not statistically significant) in males at 60 mg/kg and in females at \geq 15 mg/kg, when compared to control.) **Possible adverse effects:** There were increased clinical effects observed at all doses and increased mortality at 60 mg/kg. These data were supplemental. M. Silva, 1/26/96.

Chronic Study:

** 172 098090, "Chronic Oral Toxicity Study of Didecyldimethylammoniumchloride in Dogs", (G.E. Schulze, Hazleton Washington, Inc., 9200 Leesburg Turnpike, Vienna, VA., Report # 2545-102, 7/26/91). Didecyldimethylammoniumchloride (DDAC; 80.8% pure), was administered by gavage to purebred Beagle (4/sex/dose) at 0 (distilled water), 3, 10, or 30 mg/kg/day. Dosing at 30 mg/kg was discontinued days 31-36, then was resumed at 20 mg/kg. Dogs were dosed twice a day at volumes of 10 ml/kg. Originally reviewed (Silva, 5/12/95) as having a NOEL = 3 mg/kg/day (An increased incidence in emesis, salivation and mucoid/liquid feces was observed.) However, these effects were primarily due to the method of administration and not due to chronic effects. Therefore, the NOEL has been changed to: Chronic NOEL = 10 mg/kg/day (A slight decrease in body weight and food consumption, primarily in males was observed. There were sporadic decreases in serum albumin, total protein, cholesterol, erythrocyte count, hemoglobin and hematocrit in both sexes.) **No adverse effects. Acceptable.** (Silva, 1/22/96).

ONCOGENICITY, MOUSE

** 160 096651 "Chronic Dietary Oncogenicity Study with Didecyldimethyl-ammoniumchloride in Mice", (M.W.Gill, S.J. Hermansky & C.L. Wagner, Bushy Run Research Center, Export, PA., Report # 53-528, 2/7/91). Didecyl dimethyl ammonium chloride (DDAC, 80.8% pure) was fed in diet for approximately 18 months to CD-1[®] mice (60/sex/dose) at 0 (Ground Purina Certified Rodent Chow[®] #5002), 100, 500, and 1000 ppm. A second control group of 60/sex was also included. Data from this group were treated separately from the other control group. Chronic NOEL = 500 ppm (Both sexes had decreased bodyweights and food consumption at 1000 ppm.) Oncogenicity NOEL \geq 1000 ppm. No treatment-related oncogenic effects were observed at any dose. **No adverse effect. Acceptable.** (Green & Silva, 5/15/95).

REPRODUCTION, RAT

** 159 096650, "Two-Generation Reproduction Study in Sprague-Dawley (CD[®]) Rats with Didecyldimethylammoniumchloride Administered in the Diet", (T.L. Neeper-Bradley, Bushy Run Research Center, Export, PA., Report # 52-648, 2/1/91). Didecyldimethylammoniumchloride (80.8% pure), was fed in diet to Sprague-Dawley (CD[®]) rats (28/sex/dose) through two generations with 2 litters per generation at 0 (Purina Certified Ground Rodent Chow[®] #5002), 300, 750, and 1500 ppm. Treatment began 10 weeks prior to mating. Parental NOEL = 750 ppm (Reduced bodyweights and food consumption were observed at 1500 ppm). Reproductive NOEL = 750 ppm (Pups had reduced bodyweight gain at 1500 ppm). No adverse effect. **Acceptable.** (H. Green & M. Silva, 4/6/95).

TERATOLOGY, RAT

048 036878, "Teratologic Evaluation of Three Quaternary Compounds (Bardac-22, Bardac-20, Bardac LF)" (Food and Drug Research Laboratories, Inc., 3-11-77). Three formulations of quaternary ammonium compounds (didecyl dimethyl ammonium chloride--50%, octyl decyl dimethyl ammonium chloride--25% and dioctyl dimethyl ammonium chloride--50%) given to Wistar rats in separate experiments by oral gavage at 0, 10, 25 and 50 mg/kg/day (as formulation) on days 6-15 of gestation; 21-22 females/test article group; maternal and developmental NOELs > 50 mg/kg (HDT); No adverse effects, UNACCEPTABLE. (MTD not achieved, no individual animal data, no analysis of dosing solutions), Not upgradeable. (J. Parker, 7-24-86).

** 167 097264, "Developmental Toxicity Evaluation of Didecyldimethylammoniumchloride Administered by Gavage to CD[®](Sprague-Dawley) Rats", (T. L. Neeper-Bradley, Bushy Run Research Center, 6702 Mellon Road, Export, PA., Report # 53-534, 5/17/91).

Didecyldimethylammoniumchloride (80.8% pure, wt/wt) was administered by gavage to mated CrI:CDBR Sprague Dawley rats (25/dose) on gestation days 6 through 15 at 0 (deionized Millipore* water), 1, 10, and 20 mg/kg/day. **Maternal NOEL** = 1 mg/kg/day (Clinical signs: increased incidence of audible respiration and gasping at ≥ 10 mg/kg). **Development NOEL:** There were no developmental effects at any dose.

No adverse effect. Acceptable. (H. Green & M. Silva, 5/5/95).

230 122618, "Developmental Toxicity Dose Range-Finding Study of Didecyldimethyl ammonium chloride Administered by Gavage to CD[®](Sprague-Dawley) Rats," (Neeper-Bradley, T.L., Union Carbide, Bushy Run Research Center, Export, PA; Lab Project #: 53-533; 2/26/93).

Didecyldimethylammoniumchloride (80.8% pure, wt/wt) was administered by gavage to mated (plug-positive) Sprague-Dawley CD rats (5/dose) on gestation days 6 - 15 at 0 (deionized Millipore[®] water), 1, 12.5, 25, 37.5 & 50 mg/kg/day. **Maternal NOEL** = 12.5 mg/kg (There was a significant increase in late resorptions and a decrease in fetal weights at 50 mg/kg. Clinical observations at ≥ 25 mg/kg: audible respiration, perioral & perinasal encrustation and at ≥ 37.5 mg/kg: urogenital wetness, gasping & loose feces were reported. Bodyweights, food consumption and gravid uterine weights were decreased at ≥ 37.5 mg/kg. Necropsy findings showed increased ulcerations, mucosal hyperplasia and erosion in the non-glandular stomach at ≥ 37.5 mg/kg. **Developmental NOEL:** There were no effects at any dose. No adverse effect. These data are supplemental. M. Silva, 4/4/95.

TERATOLOGY, RABBIT

103 073130 "Developmental Toxicity Study of Didecyldimethyl ammonium chloride Administered by Gavage to New Zealand White Rabbits," (Tyl, R.W., Bushy Run Research Center, Project ID 51-590, 1-27-89). Bardac 2280 (Batch B-1889, 80.8% pure), was administered by gavage to mated New Zealand White rabbits on days 6 - 18 of gestation (day of mating = day 0 of gestation) at 0 (vehicle = deionized water), 1.0, 3.0 or 10.0 mg/kg/day (16/group). Maternal NOEL = 1.0 mg/kg (4 deaths accompanied by labored respiration, gasping, sloughing of esophageal lining and stomach, and decreased weight gain was observed at 10.0 mg/kg. At 3.0 mg/kg audible respiration, hypoactivity and decreased weight gain was observed.) Developmental NOEL = 3.0 mg/kg (An increased number of dead fetuses/litter and decreased fetal body weight at 10.0 mg/kg was observed.) **No adverse effects. Acceptable. M. Silva, 8/9/90.

GENE MUTATION

** 083 071623 "Mutagenicity Test on Didecyldimethylammoniumchloride (DDAC) in the CHO/HGPRT Forward Mutation Assay" (Young, R.R., Hazleton Laboratories America, Inc., Study No. 10141-0-435, 9-9-88). Bardac 2280 (an 80% manufacturing use product of DDAC, Lot B-1889) was assayed in a CHO/HGPRT forward mutation assay at concentrations of 0 (vehicle = deionized water), 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 10.0 $\mu\text{g/ml}$ without metabolic activation. In the first trial, the survival ranged from 105.9% to 10.7%. The second trial gave survivals ranging from 106.6% to 5.7%. Neither assay showed an increase in mutant frequency. Trials with metabolic activation were conducted at concentrations of 0, 1.0, 5.0, 10.0, 13.0, 15.0, 18.0, 20.0, 22.0 and 25.0 $\mu\text{g/ml}$. The first trial yielded survivals of 105.1% to 2.8% (at doses from 5.0 to 25.0 $\mu\text{g/ml}$). The repeat trial yielded survivals from 102.4% to 19.3% (at doses from 10.0 to 22.0 $\mu\text{g/ml}$).

Neither trial showed an increase in mutant frequency. **No adverse effect. Acceptable.** M. Silva, 8/9/90.

062 066810 "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)," (Marino, M.S.--Study Coordinator and Haworth, S.R.--Study Director, Microbiological Associates, Study No. T2389.501, 3-30-84). Micro-Emulsion Concentrate Type A (lot 4411-158-A, no detailed description) was assayed in the Ames test with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations of 0 (water), 0.01, 0.05, 0.1, 0.5 and 2.0 µg/plate. The assay was conducted in the presence and absence of metabolic activation (triplicate plating). No increase in number of revertants was observed. **No adverse effects. Not acceptable** (A mixture of two a.i.'s was used in this study.) M. Silva, 8/15/90.
EPA one-liner: Unacceptable

CHROMOSOME EFFECTS

** 157 096599 "Analysis of Metaphase Chromosomes Obtained from Bone Marrow of Rats Treated with P0151", (J.A. Allen, R.J. Proudlock & P.C. Brooker, Huntingdon Research Center, Huntingdon, England, Project # LZA 24/8761, 4/1/87). Didecyl dimethyl ammonium chloride (DDAC, 50.3% pure) was administered by gavage to CD albino rats (5/sex/sampling time) at 0 (distilled water) and 600 mg/kg. Bone marrow sampling of vehicle control and DDAC groups was performed at 6, 24, and 48 hours. The positive control, cyclophosphamide (40 mg/kg), was sampled at 24 hours. There were no treatment-related effects at any dose. Positive controls functioned as expected. **No adverse effect. Acceptable.** (H. Green & M. Silva, 5/16/95)

** 157, 304 096600, 140847 "P0151: Chromosomal Aberrations Assay with Chinese Hamster Ovary Cells *in vitro*", (M. Holmstrom, D.J. Leftwich & I.A. Leddy, Gulland Laboratories of Inveresk Research International, Musselburgh, Scotland, Report # 4236, October 1986). PO151 (Bardac 22 = 50% solution of didecyl dimethyl ammonium chloride), was used in an *in vitro* cytogenetic assay in the presence of activation (+S9) with Chinese Hamster ovary cells in duplicate at concentrations of untreated, 0 (deionised distilled water), 2, 4, 8, and 16 µg/ml. In the absence of activation (no S9), concentrations for the first replicate were untreated, 0 (deionized distilled water), 0.25, 0.5, 1.0, and 2.0 µg/ml. These levels did not produce the expected toxicity so levels for the second replicate were increased to: untreated, 0, 1.0, 2.0, 4.0, and 8.0 µg/ml. **No adverse effect either with or without S9.** Originally reviewed as not acceptable (M. Silva, 5/16/95). Upon receipt and review of the complete report it is now upgraded to acceptable. (M. Silva, 1/25/96).

DNA DAMAGE

** 083 071622 "Mutagenicity Test on Didecyldimethylammoniumchloride in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay," (Cifone, M.A., Hazleton Laboratories America, HLA Study No. 10141-0-447, 9-12-88). Bardac 2280 (an 80% manufacturing use product of didecyldimethylammoniumchloride, Batch No. B1889) was assayed for unscheduled DNA synthesis in deionized water with rat hepatocytes at concentrations of 0 (deionized water), 0.050, 0.100, 0.250, 0.500, 0.750, 1.00 and 2.00 µg/ml. Five cultures per treatment level were used (2 for cytotoxicity, 3 for the UDS assay). Fifty cells/culture were analyzed for net nuclear grain count. Survival was 74.6% or greater in the first trial and 85.6% or greater in the confirming trial. No UDS response was observed. **No adverse effect. Acceptable.** M. Silva, 8/8/90.

NEUROTOXICITY

Not required at this time

SUPPLEMENTAL STUDIES:
SUBCHRONIC

086 071626 "Subchronic Dietary Dose Range Finding Study with Didecyldimethylammoniumchloride in Mice", (Van Miller, J.P., Bushy Run Research Center, ID No. 51-507, 9-12-88). Bardac 2280 (Batch No. B-1889, purity = 80.8%) was fed to CD-1 mice (15/sex/group) in the diet at 0 (vehicle = diet), 100, 300, 600, 1000 or 3000 ppm daily for 89 day (males) or 90 days. NOEL = 600 ppm (At 1000 ppm, males showed decreased bodyweight gain. All animals at 3000 ppm died except for one male. Animals exhibited general ill health with hunched posture, emaciation, distension and/or watery contents of the intestines. Death was attributed to treatment related malnutrition and dehydration). NOAEL = 1000 ppm (Bodyweight effects were minimal at 1000 ppm, where death occurred at 3000 ppm in both sexes). **Supplemental.** Study is adequate to set dose levels for an oncogenicity study. M. Silva, 7/26/90.

084 071624 "Ninety-Day Dietary Subchronic Oral Toxicity Study with Didecyldimethylammoniumchloride in Rats", (Van Miller, J.P., Bushy Run Research Center, Project ID 51-506, 9-6-88) Bardac 2280 (Batch B-1889, 80.8% pure) was fed in diet to Sprague-Dawley CD rats (15/sex/group) at 0 (vehicle = diet), 100, 300, 600, 1000 or 3000 ppm for 90 (males) or 91 (females) days. NOEL = 1000 ppm (At 3000 ppm there was 80% mortality (by day 17) accompanied by decreased body weight, fluid or gas filled intestines, general ill health, emaciation, hunched posture and altered clinical chemistry. Death was attributed to ileus and shock. Bardac 2280 may have been slightly corrosive to the digestive tract. Early death was more of an acute than chronic effect). The study was adequate to determine dose levels for a chronic study. **Supplemental.** M. Silva, 7/31/90.

085 071625 "Ninety-Day Subchronic Dermal Toxicity Study with Didecyldimethylammoniumchloride in Rats," (Gill, M.W. and Van Miller, J.P., Bushy Run Research Center, Lab ID 51-554, 10-7-88). Bardac 2280 (batch No. B-1889, 80.8% pure), was applied to the clipped backs of Sprague Dawley rats (15/sex/dose) for 6 hours (occluded), 5 days/week, for 13 weeks at concentrations of 0 (water), 0.1, 0.3 and 0.6% (w/w), which was equivalent to 0, 2, 6 and 12 mg/kg. **Possible adverse effect indicated.** Dermal NOEL = 2 mg/kg (Skin irritant effects, such as epidermitis and dermatitis were observed in males at 12 mg/kg/day and in females at ≥ 6 mg/kg/day. Females at 12 mg/kg/day also experienced focal hemorrhages, vacuolar degeneration and ulceration of the skin. Both sexes at ≥ 6 mg/kg/day showed erythema and edema at the site of Bardac 2280 application during certain time periods of the study.) No systemic toxicity was observed nor were other measured parameters affected by test chemical administration. **Supplemental.** M. Silva, 7/27/90.

SPECIAL TOXICOLOGY - ANIMAL METABOLISM

127 088014, "Absorption, Distribution, Metabolism and Excretion Studies of Didecyldimethylammoniumchloride (DDAC) in the Rat" and an addendum (two separate reports with the same title and record #; Paul Lin and Sami Selim were authors of the original report; Sami Selim authored the addendum, Biological Test Center; BTC Study No. P01421 and the addendum, 12/1/89). DDAC (40% aqueous in both radiolabeled [^{14}C] and nonradiolabeled form), used in a definitive pharmacokinetic study to determine absorption, distribution and excretion and

was administered orally (single dose), by gavage, to Charles River CD (CrI CD(SD)Br--5/sex/group) in 3 dose regimens: 1) A single low dose (5 mg/kg), 2) a repeated low dose in diet containing 34 ppm "cold" in the feed daily for 14 days, followed by a 5 mg/kg dose of [14C]-DDCA (9.01 mCi/mmol, and 99% radiochemical purity) or 3) a single high dose of 50 mg/kg. Excretion of radioactivity was shown to occur primarily in the feces (89-99%), some in urine (< 2.5%), and an insignificant amount was expired. Highly ionic DDAC is not readily absorbed from the GI tract. In the addendum the metabolic profile was determined in a 2 step experiment. First, another group of rats (10 male Charles River CD (CrI CD(SD)Br) were treated with [14C]-DDAC at 50 mg/kg in order to obtain enough [14C] residues to use as standards. The [14C] metabolites were characterized by TLC, HPLC and MS. The second part of the experiment involved using the "standard" metabolic profiles to analyze the metabolites from feces samples obtained in the initial study. It was shown that metabolism tends to be sex specific. Females metabolize the parent compound more so than males. Metabolism, which may be microbial in nature, involved the oxidation of the 2 decyl side chains to form hydroxy and hydroxyketo derivatives. Modification of methyl substituents was not evident. (Kishiyama & Silva, 8/8/90).