UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

DATE: May 17, 2016

SUBJECT: **DDAC:** Summary of Hazard and Science Policy Council (HASPOC) Meeting of March 3, 2016: Recommendation on the Requirement for Neurotoxicity (Acute and Subchronic) and Immunotoxicity Studies.

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Registration No.: NA
Regulatory Action: NA
Case No.: N/A
CAS No.: 7173-1-5, 5538-94-3, 32426-11-2, 84540-07-8, 68607-28-3
40 CFR: N/A

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THROUGH: Jaime D'Agostino, Ph.D., Co-Chair
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TO: LCDR Jonathan Leshin, Ph.D.
Steve Weiss, Branch Chief
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MEETING ATTENDEES

HASPOC Members: Anna Lowit, Elissa Reaves, Jaime D'Agostino, Jeff Dawson, John Kough, Jonathan Chen, Jonathan Leshin, Kelly Lowe, Michael Metzger, P.V. Shah, Ray Kent, Sarah Gallagher, Uma Habiba

Presenters: Jonathan Leshin

Other Attendees: Jenny Tao, Julie Van Alstine, Katelynn King, Kristin Rickard, Tim Dole, Tim Leighton, Rachel Ricciardi

I. PURPOSE OF MEETING

The Risk Assessment and Science Support Branch (RASSB) of the Antimicrobials Division is currently preparing a preliminary workplan for registration review in support of didecyl dimethyl ammonium chloride (DDAC) Group I quaternary ammonium compounds. The toxicology database for DDAC is complete except for the neurotoxicity (acute and subchronic) and immunotoxicity studies that are required in accordance with the current 40 CFR Part 158W Toxicology Data Requirements. The Hazard and Science Policy Council (HASPOC) met on March 3, 2016 to discuss the need for these studies in support of registration review.

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATIONS

Pursuant to PR Notice 88-2, grouping of quaternary ammonium compounds was allowed, based on chemical structure, into 4 broad categories: Group I quaternary ammonium compounds (alkyl or hydroxy alkyl substituted compounds) (DDAC, or didecyl dimethyl ammonium chloride, as representative); Group II non-halogenated benzyl substituted quaternary ammonium compounds (ABDAC as representative); Group III di- and trichlorobenzyl substituted quaternary ammonium compounds; and Group IV, quaternary ammonium compounds with unusual substituents.

The Group I aliphatic alkyl quaternary compounds include five compounds that are structurally similar quaternary ammonium compounds characterized by having a positively charged nitrogen covalently bonded to two alkyl group substituents (at least one C8 or longer) and two methyl substituents. In finished form, these quaternary compounds are salts with positively charged nitrogen (cation) balanced by a negatively charged atom (anion). The anion for the quaternary compounds in this group is chlorine or bromine. Since DDAC is the representative chemical for the Group I quaternary ammonium compounds, hazard data generated for DDAC is considered to be representative of the hazards associated with all chemicals assigned to this class.

Chemicals in this group are used as algicides, bacteriocides, fungicides, fungistats, viricides, tuberculocides, wood preservatives, insecticides, microbicides, microbiostats, molluscides, deodorants, disinfectants, and sanitizers. There are dietary exposures for DDAC, including food contact surfaces, treatment of mushroom houses, and application to food grade eggs. Residues may also result from food contact with treated surfaces, such as food utensils, countertops, equipment, and appliances. Food packaging and beverage bottling uses also occur. DDAC formulations are used in swimming pools, spas, cooling water towers, oil field drilling muds and packing fluids, small process water systems, humidifiers, mushroom farms, citrus farms, swine/poultry/turkey farms, dressing plants, farrowing barns, and flower shops. There are uses on medical equipment and in other related health and home care facilities. It is used in food handling/storage establishments, equipment, and premises. DDAC formulations are diluted in water to treat hard nonporous surfaces in institutional, commercial, industrial, and residential settings by fogging, immersion, wiping, mopping, aerosol/trigger spray, and low-and high-pressure spray. Some impregnated wipes are dampened with water prior to use while others are

pre-moistened. For the treatment of wood, DDAC is applied by a blender/spray system, dip tank, spray box, or pressure treatment.

DDAC has moderate acute toxicity via the oral and inhalation routes (Toxicity Category II), but it is only slightly toxic via the dermal route (Toxicity Category III). It causes severe eye and skin irritation (Toxicity Category I) but it is not a dermal sensitizer. The majority of studies for DDAC are old and have NOEL/LOELs, instead of NOAEL/LOAELs.

Following oral administration, the most sensitive effect of DDAC appears to be local irritation of the gut. All oral studies found decreases in body weight, body weight gain, and food efficiency/consumption (where measured). Based on the 90-day oral rat study, mortality becomes significant at 175.4 mg/kg/day in females and 225 mg/kg/day in males, along with gross pathology in the stomach (hemorrhage and emaciation), decreased spleen size, abnormal cecum contents, and changes in the mesenteric lymph node (lymphoid hyperplasia). These effects are present at varying levels in the moribund sacrifices, deaths, and terminal sacrifices. These effects were not observed at 60.7/74.3 mg/kg/day (m/f) and the rats were not dosed as high in the other studies.

The decreased body weights were most likely attributable to the constant and direct irritation of the gastric lining, which is consistent with the effects in the chronic dog study, which were largely emesis and soft stool/mucoid stool, along with decreased body weight gain, food consumption, and food efficiency. Decreased body weights were also observed in the developmental studies in rats and rabbits, the reproduction and fertility study in rats, the chronic/cancer study in rats, and the carcinogenicity studies in mice.

The developmental rat and rabbit studies identified maternal endpoints based on decreased body weight and clinical signs including hypoactivity, audible and labored breathing, and gasping. There was no developmental endpoint identified in the rat study; but in the rabbit study, the endpoint was based on decreased fetal body weight. In the reproduction and fertility study, the parental NOAEL/LOAEL was based on decreased body weight/bodyweight gain and food consumption. The reproduction NOAEL/LOAEL was observed at the same dose, and is based on decreased mean pup body weight and body weight gain during the postnatal period.

Following dermal exposure, irritation is the predominant effect with corresponding histopathological findings in the skin. In a 90-day dermal study, there were no systemic effects observed. Hyperkeratosis, erythema, and exfoliation were present in both males and females. Females appeared more sensitive to the irritation effects, and they also exhibited acathosis, epidermitis, dermitis, and ulceration.

DDAC is not considered mutagenic. There are two cancer studies, one in mice and a combined chronic/cancer study in rats. In mice, doses up to 155.5 (m)/ 193.1 (f) mg/kg/day did not induce effects on survival, hematology, clinical signs, organ weights, gross, or histopathology. The major effects noted were decreases in body weight and body weight gain. There was no evidence of carcinogenicity at the doses tested. In the combined chronic/carcinogenicity study in rats, doses were selected based on the 90-day oral study. In this study, a chronic toxicity (NOAEL/LOAEL) was set based on decreases in body weight and body weight gain as well as

increased incidences of non-neoplastic lesions in the mesenteric lymph nodes (sinusoidal blood, hemosiderosis, and histiocytosis). DDAC was not considered carcinogenic at the doses tested.

In the 28-day inhalation toxicity with 2 week recovery study in rats, pulmonary effects and decreased body weight were observed at 0.0005 mg/L in males and 0.0015 mg/L in males and females. In the high dose group, body weight and lung weights were considered reversible during the recovery period. Histopathology findings included ulceration of the stratified squamous epithelium of the nasal cavity and degeneration of the olfactory epithelium as the major effects along with increased mucous production. These effects all occurred in the rostral section, with the olfactory findings being most predominant in sections II and III where they represent the rostral extension of the olfactory epithelium. The LOAEC was 0.00008 mg/L and a NOAEC was not identified. An unreviewed open literature study (Lim and Chung, 2014) evaluated inhalation exposure for 2 weeks, and represents the only literature study of note on the chemical available in PubMed. At the highest dose tested (0.0036 mg/L), there were decreased body weights relative to controls. Histopathology in the lung appears to include inflammatory cell infiltration and interstitial pneumonia at both 0.0036 and 0.0006 mg/L, along with mild changes in the bronchoalveolar cell differentiation counts and cell damage parameters from lavage fluid. It does not appear that the nasal cavity was examined.

III. STUDY WAIVER REQUEST

a. Neurotoxicity Studies

Acute neurotoxicity (ACN) and subchronic neurotoxicity (SCN) studies are required in the 2007 revised 40 CFR Part 158 Toxicology Data Requirements because they provide important scientific information on potential nervous system effects from pesticide exposure. These studies can provide data on a wide range of functional tests for evaluating neurotoxicity including sensory effects, neuromuscular effects, learning and memory, and histopathology of the nervous system.

Considering whether the ACN and SCN studies should be required for DDAC, the HASPOC used the following WOE approach:

1. **Evidence for potential neurotoxicity in the DDAC database of toxicology studies:** There were no clinical signs or evidence of neurotoxicity in the DDAC database.

2. **Evidence for neurotoxicity in the database of other similar chemicals:** There are no data available for the other chemicals in this class as DDAC is considered to be representative of the Group I quaternary ammonium compounds.

3. **Risk assessment considerations:** An acute dietary endpoint was selected based on the acute oral study. The available data indicate that neurotoxicity is of low concern for DDAC and that the ACN/SCN would not likely provide a lower POD for the risk assessment. All existing data indicates irritation as the mechanism of toxicity for Group I quaternary ammonium compounds.

HASPOC recommends, based on a WOE approach, that the acute and subchronic neurotoxicity studies (ACN and SCN) are not required for DDAC. This approach considered all of the available hazard and exposure information, including: (1) no evidence of neurotoxicity in the toxicity database for DDAC; (2) the primary toxicity of this class of chemicals is point of contact irritation; and (3) the ACN/SCN are not likely to identify a lower POD or a more sensitive endpoint for the risk assessment.

b. Immunotoxicity

1. **Evidence for potential immunotoxicity in the DDAC database of toxicology studies:** The effects of the chemical are likely related to the irritation effects of the chemical. The decreased spleen size is considered secondary to weight loss. The hyperplasia in the mesenteric lymph node is considered secondary to the irritation of the chemical.

Table 1. Summary of DDAC Immunotoxicity Potential in Toxicology Studies.

Parameter	Findings
Hematology Indicators (WBC changes)	None
Clinical Chemistry Indicators (A/G Ratio)	None
Organ Weight Indicators (Spleen, Thymus)	None
Histopathology Indicators (Spleen, Thymus, Lymph nodes)	Decreased spleen size (secondary to decreased body weight and mortality) Increased incidences of non-neoplastic lesions in the mesenteric lymph nodes (secondary to irritation)
Toxicity Profile (Target Organs)	Skin (dermal), lungs (inhalation)

2. **Evidence for potential immunotoxicity from the database of toxicology studies for other pesticides or structure activity relationship (SAR) chemicals -retrospective analysis:** There are no data available for the other chemicals in this class as DDAC is considered to be representative of the Group I quaternary ammonium compounds.

Based on a WOE approach, the HASPOC recommends that the immunotoxicity study is not required at this time for DDAC. This approach considered all of the available hazard and exposure information, including: (1) the known target organs of DDAC are the skin and lung given that the chemical acts as a point of contact irritant; (2) the changes in spleen weights occurred secondary to decreased body weight; and (3) the most sensitive endpoints are based on irritation which is considered protective of any potential immunotoxicity.

IV. HASPOC RECOMMENDATIONS

Based on a WOE approach, considering all available hazard and exposure information for DDAC, the HASPOC concludes that the acute and subchronic neurotoxicity and immunotoxicity studies **are not required** at this time.