Proposed Registration Decision PRD2024-06

# Didecyl Dimethyl Ammonium Chloride (DDAC), Acticide DDQ 50-E

(*publié aussi en français*)

**31 May 2024**

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2 Constellation Drive
8th floor, A.L. 2608 A
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
pmra.publications-arla@hc-sc.gc.ca

Information Service:
1-800-267-6315
pmra.info-arla@hc-sc.gc.ca

Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2024-6E (print version)
H113-9/2024-6E-PDF (PDF version)

# Table of Contents

# Overview

## Proposed Registration Decision for Didecyl Dimethyl Ammonium Chloride (DDAC)

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of the technical, Acticide DDQ 80-F, and the end-use product, Acticide DDQ 50-E, containing the technical grade active ingredient didecyl dimethyl ammonium chloride (DDAC), for use as a material preservative in polymers.

DDAC is currently registered for use in a wide range of applications, including hard surface sanitization, industrial process fluids, and the antisapstain protection of wood. For details, see Proposed Re-evaluation Decision PRVD2008-27, *Didecyl Dimethyl Ammonium Chloride Cluster (DDAC)* and Re-evaluation Decision RVD2009-07, *Didecyl Dimethyl Ammonium Chloride Cluster (DDAC)* and also, PRVD2016-24 and RVD2017-09, *Antisapstain and Joinery Uses of Didecyl Dimethyl Ammonium Chloride (DDAC)*.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of DDAC and Acticide DDQ 50-E.

## What does Health Canada consider when making a registration decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to individuals and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include precautionary measures on the product label to further reduce risk.

---

1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children). They also consider the unique characteristics of organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and pest management page on Canada.ca.

Before making a final registration decision on DDAC and Acticide DDQ 50-E, Health Canada's PMRA will consider any written comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on DDAC and Acticide DDQ 50-E, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

For more details on the information presented in this Overview, please refer to the Science evaluation of this consultation document.

## What is Didecyl Dimethyl Ammonium Chloride (DDAC)?

DDAC is a biocide registered for the control of algae, bacteria, fungi or molluscs in the following use sites: indoor hard surfaces (for example, floors, walls, countertops), other indoor surfaces (for example, carpet, laundry), industrial process fluids (for example, open cooling water tower system, oil field water flood or salt water disposal systems, recirculating water cooling towers) and the antisapstain protection of wood. DDAC damages microbial cell membranes, leading to their death.

## Health considerations

### Can approved uses of DDAC affect human health?

**Acticide DDQ 50-E, containing DDAC, is unlikely to affect your health when used according to proposed label directions.**

Potential exposure to DDAC may occur when handling and applying the end-use product, and when coming into contact with treated surfaces. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed.

---

3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The dose levels used to assess risks are selected to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose level at which no effects are observed. The health effects noted in animals occur at dose levels more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, DDAC was of low acute toxicity via the dermal route. It was highly acutely toxic via the oral route, and corrosive to eyes and skin. Based on its corrosive nature, DDAC is also considered highly acutely toxic via inhalation. Evidence from the published literature suggests that DDAC causes an allergic skin reaction. As a result of these findings, the signal word "DANGER" and hazard statements "POISON", "CORROSIVE TO EYES AND SKIN", and "POTENTIAL DERMAL SENSITIZER" are required on the label.

The acute toxicity of the end-use product, Acticide DDQ 50-E, was based on the acute toxicity of the active ingredient DDAC. Therefore, the signal word "DANGER" and hazard statements "POISON", "CORROSIVE TO EYES AND SKIN", and "POTENTIAL DERMAL SENSITIZER" are also required on the end-use product label.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential for DDAC to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on the respiratory tract, delayed fetal development, general signs of ill health, and allergic skin reactions. There was no evidence of increased sensitivity of the young compared to adult animals. The risk assessment protects against the effects noted above and other potential effects by helping to ensure that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

**Occupational risks from handling Acticide DDQ 50-E**

**Occupational risks are not of health concern when Acticide DDQ 50-E is used according to the proposed label directions, which include protective measures.**

A risk assessment conducted for individuals mixing and adding Acticide DDQ 50-E to polymers, dispersions, lattices, solutions, and resins for the manufacturing of household/institutional laundry detergents, and individuals entering these facilities, indicated that risk is not of concern when the product is used according to label directions.

Workers adding Acticide DDQ 50-E to polymers, dispersions, lattices, solutions, and resins, can come in direct contact with Acticide DDQ 50-E on the skin or through inhalation. Therefore, the label will specify that anyone mixing or loading Acticide DDQ 50-E and performing cleaning and repair activities, must wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, chemical-resistant footwear, protective eyewear (goggles or face shield) and a respirator with a NIOSH-approved organic-vapour-removing cartridge (with a prefilter) approved for pesticides or a NIOSH-approved canister approved for pesticides.

There is potential for dermal exposure to downstream workers in the facilities where polymers treated with Acticide DDQ 50-E are manufactured. Since these workers are expected to be wearing personal protective equipment (PPE) as specified in the regulations regarding worker health and safety, it is likely that this will limit potential exposure when conducting postapplication activities.

In addition, there is potential for exposure to secondary occupational workers handling laundry detergent containing the preserved polymers, in commercial (large or small scale) laundry service facilities (for example, handling laundry from hotels, hospitals, restaurants). The risk assessment conducted indicated that the risk to secondary workers is not of concern when the laundry detergent is manufactured according to label directions.

**Risks in residential and other non-occupational environments**

**Risks in residential and other non-occupational environments are not of health concern when Acticide DDQ 50-E is used according to the proposed label directions.**

Adults, youth and children can come into direct contact with DDAC residues when adding laundry detergent to laundry or when wearing clothing laundered with the detergent. Taking into consideration the label statements and the duration of exposure, the risks to individuals handling laundry detergent, and wearing clothing laundered with the detergent are not of health concern.

**Risks to bystanders**

**Bystander risks are not of health concern when Acticide DDQ 50-E is used according to the proposed label directions.**

Bystander exposure is expected to be negligible for industrial scenarios where Acticide DDQ 50-E is used in the manufacturing of the laundry detergent. Therefore, health risks to bystanders are not of concern.

## Environmental considerations

### What happens when DDAC is introduced into the environment?

**When used according to label directions, the risks associated with the use of Acticide DDQ 50-E, containing DDAC, are acceptable from the viewpoint of environmental protection.**

DDAC is not expected to build-up in the environment, and exposure to non-target organisms is expected to be low. Under the use pattern proposed, DDAC is not expected to present a risk to non-target terrestrial and aquatic organisms. When used as a material preservative in accordance with the label directions and the required precautions, the product Acticide DDQ 50-E is expected to pose acceptable risks to the environment.

## Value considerations

### What is the value of Acticide DDQ 50-E?

**Acticide DDQ 50-E is an effective material preservative, capable of preventing the growth of bacteria, yeast, and mould in polymer emulsions.**

Water-based polymer emulsions, when contaminated by bacteria or fungi, provide an excellent environment for microbial life to grow. Acticide DDQ 50-E will help prevent spoilage of natural and synthetic polymer emulsions and dispersions by bacteria and fungi during the manufacturing process, and during bulk storage or transport. There are a number of other active ingredients currently registered as in-can polymer preservatives. DDAC will provide manufacturers an alternative that may help address issues with material compatibility, cost, microbial resistance or active ingredient availability.

## Measures to minimize risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the labels of Acticide DDQ 80-F and Acticide DDQ 50-E to address the potential risks identified in this assessment are as follows.

### Key risk-reduction measures

### Human health

Since there is potential for workers to come into direct contact with DDAC through the dermal or inhalation route, workers mixing and loading Acticide DDQ 50-E and performing cleaning and repair activities are required to wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, chemical-resistant footwear, protective eyewear (goggles

or face shield) and a respirator with a NIOSH-approved organic-vapour-removing cartridge (with a prefilter) approved for pesticides or a NIOSH-approved canister approved for pesticides.

**Environment**

- Precautionary label statements are required to inform users that the DDAC end-use product Acticide DDQ 50-E is toxic to aquatic organisms and to update the proposed label with the new effluent label statement.
- Storage and disposal statements are required.

## Next steps

Before making a final registration decision on DDAC and Acticide DDQ 50-E, Health Canada's PMRA will consider any written comments received from the public in response to this consultation document up to 45 days from the date of publication (31 May 2024) of this document. Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

## Other information

When Health Canada makes its registration decision, it will publish a Registration Decision on DDAC and Acticide DDQ 50-E (based on the Science evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

# Science evaluation

## Didecyl Dimethyl Ammonium Chloride (DDAC), Acticide DDQ 50-E

## 1.0 The active ingredient, its properties and uses

No chemistry data were provided or required. The technical product (Acticide DDQ 80-F) is guaranteed to contain DDAC at 76.77% and the end-use product (Acticide DDQ 50-E) to contain DDAC at 50%. A review of the chemistry was previously published in the Proposed Re-evaluation Decision PRVD2008-27 and Re-evaluation Decision RVD2009-07, *Didecyl Dimethyl Ammonium Chloride Cluster (DDAC)* and also, PRVD2016-24 and RVD2017-09, *Antisapstain and Joinery Uses of Didecyl Dimethyl Ammonium Chloride (DDAC)*.

### 1.1 Directions for use

Acticide DDQ 50-E is added to the polymer material during the manufacturing process. It provides long-term protection during transportation and bulk storage, when used at rates between 0.02% and 0.2% by weight. This equates to a DDAC concentration of 100 ppm to 1000 ppm.

### 1.2 Mode of action

DDAC is an effective broad-spectrum antimicrobial quaternary ammonium compound, which kills microorganisms by disrupting lipid bilayer membranes. DDAC molecules penetrate into the cytoplasmic membrane, which leads to the leakage of the intracellular contents, and ultimately cell lysis.

## 2.0 Methods of analysis

Please refer to PRVD2008-27 and PRVD2016-24 for the detailed review of the methods of analysis.

## 3.0 Impact on human and animal health

### 3.1 Toxicology summary

The active ingredient, DDAC, is a quaternary ammonium compound. The cationic portion of DDAC acts as a surfactant and kills microbes by disrupting cell membranes.

A detailed review of the toxicology database for DDAC was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The majority of the toxicology studies conducted with DDAC were previously submitted to, and reviewed by, the PMRA. An updated review of these studies was conducted for the purposes of assessing the request to expand the use of DDAC to material preservatives. In addition, the results of a recently conducted 28-day inhalation toxicity study in rats were

incorporated into the hazard assessment, as were results of relevant studies located in the published scientific literature. Many studies were conducted with test materials containing 80% DDAC (identified as BARDAC 2280) or 50% DDAC (identified as BARDAC 22) in distilled water. In all in vivo studies, the administered doses were adjusted for purity of DDAC and the reported dose levels represent actual intake levels as mg DDAC/kg bw/day. The required studies were carried out in accordance with accepted international testing protocols and Good Laboratory Practices (GLP) in place at the time of study conduct. The scientific quality of the data is acceptable, and the database is considered adequate to characterize the potential health hazards associated with DDAC.

In the submitted guideline toxicokinetics study, DDAC radiolabelled with $^{14}C$ in a methyl group was administered via a single low or high gavage dose, or as a single gavage low dose after animals were administered a diet containing a low level of non-radiolabelled DDAC for 15 days. In this study, oral absorption of DDAC appeared to be very low, with 89–99% of the administered dose excreted via the feces and only 1.2–2.4% via the urine. However, there was no assessment of biliary elimination in this study to determine the enterohepatic circulation and subsequent elimination of absorbed DDAC via the bile. Very low oral absorption was confirmed in a review of the hazard information for DDAC published in the scientific literature (PMRA# 3550218), in which it was also reported that DDAC was found to be poorly absorbed in rats via the oral route, with total oral absorption estimated to be between 3% and 7% based on urinary (0.9–3.2%) and biliary (1.8–4.0%) excretion. The administered radioactivity was widely distributed to tissues in the available guideline toxicokinetic study; however, residues in tissues were very low (less than 0.7% of the administered dose) at seven days after administration of the radiolabelled gavage dose. Analysis of fecal radioactivity indicated that majority of the eliminated radiolabel was associated with unchanged DDAC, with identification of four minor fecal metabolites formed from oxidative modification of the decyl side chain.

DDAC was highly acutely toxic via the oral route in rats, and of low acute dermal toxicity in rabbits. Due to the corrosive nature of DDAC, the requirement for acute inhalation toxicity testing has been waived, and DDAC is considered highly acutely toxic via the inhalation route. In rabbits, DDAC has been shown to be corrosive to eyes and skin.

There is conflicting information regarding the dermal sensitization potential of DDAC. The available guinea pig assay on file with the PMRA was conducted in 2004 according to OECD guidelines and yielded negative results. In this study, a solution of 80% DDAC in distilled water was not a dermal sensitizer in guinea pigs tested with the Buehler method using induction concentrations of 0.75%, 0.5%, and 0.25% for weeks 1, 2, and 3, respectively, and a challenge concentration of 0.1%. Although negative results were observed in the Buehler test, this method is known to be less sensitive at detecting dermal sensitizers than the maximization test in guinea pigs, as reported in the OECD Test Guideline 406 for skin sensitization.

The more recent literature provides evidence that DDAC may cause allergic and hypersensitivity reactions in animals and humans. In particular, DDAC was tested in mice using a modified local lymph node assay (LLNA) in a study in the published literature (PMRA# 3550096). A concentration-dependent increase in lymphocyte proliferation was observed with a calculated

$EC_3$ value of 0.17%, representing a threshold for induction of dermal sensitization. The results of this study suggested that the proliferative immune response occurred at a non-irritating dose level, based on an evaluation of ear thickness, and that DDAC induces a T-cell or TH1-mediated hypersensitivity response.

Some irritants induce a low-level proliferation in the LLNA that may be differentiated from sensitizers by assessing the B220 + cells or IgG+/IgM+ B cells in the draining lymph node (PMRA# 3550225). The up-regulation of CD86 and HLA-DR on monocyte derived dendritic cells could also differentiate allergens and irritants. Moreover, the THP-1 cell line-based human cell line activation test (h-CLAT) can also be used in this regard. In an in vitro dermal sensitization study in the published literature (PMRA# 3550103), DDAC in ethylene glycol tested positive for dermal sensitization in the h-CLAT assay, with potency mitigated by increasing the proportion of ethylene glycol. These in vitro results further support the possibility that DDAC is inducing a sensitivity reaction and that the observed results are not due solely to the irritating nature of the compound.

The literature also includes studies in which allergic contact dermatitis of DDAC in humans was evaluated via patch testing as well as case studies describing allergic reactions in individuals under various circumstances. A threshold for dermal sensitization could not be elucidated from these studies, but their results provide evidence supporting the potential for DDAC to cause allergic contact dermatitis. Based on a review of the available evidence, DDAC will be classified as a potential dermal sensitizer, and a quantitative assessment of the risk of the general public developing a dermal sensitization response from contact with DDAC-containing products was conducted.

The acute toxicity profile of Acticide DDQ 50-E was based on that of the active ingredient DDAC. Therefore, Acticide DDQ 50-E is considered to be highly acutely toxic via the oral and inhalation routes, of low acute dermal toxicity, corrosive to eyes and skin, and a potential dermal sensitizer.

Results from subchronic and long-term oral toxicity studies indicate that DDAC does not elicit any specific target organ toxicity. The most prominent effects observed in the database reflect the highly irritating nature of this class of chemicals. Effects indicative of more generalized toxicity were observed in rats, mice and dogs, evident as decreases in body weight and body weight gain. Dogs dosed with DDAC via gavage for one year exhibited an increase in emesis and soft feces. Clinical signs of toxicity were noted in the 90-day dietary studies in rats and mice, including emaciation and hunched posture, with mortality also occurring at high dose levels. Additionally, lesions of the mesenteric lymph nodes and hyperplasia of the bile duct were observed in rats after two years of dietary dosing. Longer-term dietary dosing in rats and mice resulted in effects on body weight and impaired general condition at lower dose levels than in the 90-day studies, suggesting an increase in toxicity with prolonged duration of dosing.

In a 90-day dermal toxicity study in rats, no systemic effects were noted up to the highest dose tested, but severe irritation was noted at all dose levels. In a recently conducted 28-day guideline inhalation toxicity study in rats, effects on the respiratory tract were observed down to the lowest

concentration tested following nose-only exposure. Additional inhalation toxicity studies in which rats were whole-body exposed to DDAC for 14 or 90 days were found in the published scientific literature. In these supplemental studies, respiratory tract effects were observed at higher exposure concentrations than in the guideline study. Additional studies in the published scientific literature, examined pulmonary toxicity and inflammation in rats and mice following a single intratracheal instillation of DDAC with various protocols. Overall, these supplemental studies demonstrated that direct exposure of the respiratory tract to DDAC resulted in pulmonary cytotoxicity and inflammation, which led to pulmonary remodelling and fibrosis and a compromised pulmonary defense system.

No evidence of carcinogenic potential was observed in the long-term dietary studies conducted with DDAC in the rat or the mouse. Based on the results of a full battery of genotoxicity studies, DDAC was determined to be non-genotoxic.

In the oral gavage developmental toxicity studies in rats and rabbits, maternal animals exhibited clinical signs of toxicity, such as audible respiration and hypoactivity, at the same dose levels that resulted in delayed ossification of thoracic centra and sternebrae in rat fetuses and incomplete ossification of the parietal bone and small gallbladder in rabbit fetuses. At higher dose levels, skeletal variations were observed in rats and reduced fetal survival was observed in rabbits in the presence of more severe maternal toxicity in the form of clinical signs of ill health in maternal rats and deaths of maternal rabbits.

No treatment-related effects were observed on the reproductive parameters assessed in the dietary 2-generation reproductive toxicity study in rats, which included mating, gestation and fertility indices, live births, sex ratio, and birth weight. Treatment-related effects in offspring were limited to reduced body weight during the latter part of the pre-weaning period, which occurred at the same dose level causing body weight reductions and histiocytosis and hemosiderosis of the lymph nodes in parental animals.

Overall, the developmental and reproductive toxicity studies did not provide evidence of increased sensitivity of the young when compared to the adult animal, and serious findings were limited to reduced fetal survival in the rabbit developmental toxicity study at a dose level that also caused maternal mortality. These studies were conducted according to test guidelines in place at the time the study was conducted and not according to currently accepted test guidelines that include a longer dosing period in the developmental toxicity studies and more robust assessment of endocrine and reproductive endpoints in the reproductive toxicity studies. The noted limitations were determined to be of little consequence to the hazard characterization of DDAC given the absence of particular concerns for these endpoints when considering the entirety of the available toxicology database for DDAC, the known hazard characteristics of this class of chemicals in that the toxic effects are predominantly related to their highly irritating nature, and the calculated margins between the selected toxicology reference values and the dose levels at which effects on reproduction and development were noted. Studies in the literature have shown neural tube defects and impaired fertility in mice exposed to commercial disinfectants containing DDAC and another quaternary ammonium compound, alkyl dimethyl benzyl ammonium chloride (ADBAC). However, the results of those studies were confounded

by the fact that a formulated product was used as the test material and ambient exposure to quaternary ammonium compounds was not entirely controlled for in all experiments. The results were further limited by the use of only one dose level for some experiments, as well as unclear reporting. Regardless, the dose levels at which effects on development or fertility in mice were observed in those studies were much higher than those used as the points of departure in the human health risk assessment of DDAC.

The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 1. Results of the toxicology studies conducted on laboratory animals with DDAC are summarized in Appendix I, Table 2.

### 3.1.1 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.[5]

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies including a multi-generation reproductive toxicity study in rats, and developmental toxicity studies in rats and rabbits. While these studies were conducted according to older test guidelines and are not completely compliant with modern standards, the concern for any limitations in the protocol or assessments was low, and the studies were considered adequate to characterize the potential reproductive and developmental toxicity of DDAC.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of fetuses or offspring compared to parental animals in the dietary reproductive and gavage prenatal developmental toxicity studies. Effects observed in offspring in the 2-generation reproductive toxicity study were limited to reduced body weights and body weight gains towards the latter part of the pre-weaning period at a dose level that also resulted in parental effects in the form of reduced body weights and body weight gains as well as effects on the lymph nodes. In the rat developmental toxicity study, delayed fetal ossification occurred in the presence of audible respiration in maternal animals, with skeletal variations noted at the highest dose level tested, at which signs of more significant maternal toxicity were observed, such as gasping, decreased body weight gain, and stomach ulcerations. In the rabbit, small gallbladder, considered a variation, as well as incomplete ossification of the parietal bone were noted at a dose level that resulted in reduced body weight gain, audible respiration, hypoactivity, and discolouration of the stomach and liver in maternal animals.

---

[5] SPN2008-01, *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides.*

At the highest dose level tested in the rabbit, increased fetal mortality was observed, along with reduced fetal body weight. However, this dose level also resulted in the death of several maternal animals, and clinical signs such as gasping and laboured breathing.

Overall, the database is adequate for determining the sensitivity of the young. There is a low level of concern for sensitivity of the young as effects in the young are well-characterized and occurred in the presence of maternal toxicity. The concern for the serious fetal effects at the highest dose level tested in the rabbit was tempered by the presence of significant maternal toxicity. On the basis of this information, the *Pest Control Products Act* factor (PCPA factor) would be reduced to threefold if this endpoint was used for the point of departure for risk assessment. However, the toxicology reference values selected for risk assessment provide an intrinsic margin to the endpoint of increased fetal mortality. Consequently, the PCPA factor was reduced to onefold.

## 3.2 Toxicology reference values

### 3.2.1 Route and duration of exposure

Exposure is expected to be mainly via the dermal and inhalation routes for mixers and loaders in manufacturing facilities, postapplication workers, secondary handlers (professional handlers for industrial and institutional laundry detergents) and residential handlers (household laundry detergents). Exposure is also expected through the dermal route for adults, youth and children wearing laundered clothing and incidental oral route for children (1 to <2 years old) from mouthing laundered clothing/linens. The exposure durations are expected to be long term.

### 3.2.2 Occupational and residential toxicology reference values

**Long-term dermal – adults (greater than 16 years old) and youth (11-16 years old) (occupational and residential)**

For the long-term dermal risk assessments for adults and youth, the developmental no observed adverse effect level (NOAEL) of 1 mg/kg bw/day from the oral developmental toxicity studies in rats and rabbits was selected. At dose levels of 10 mg/kg bw/day in the rat and 3 mg/kg bw/day in the rabbit, delayed ossification and increased variations were observed in the presence of maternal toxicity. The existing short-term dermal toxicity study did not address the endpoint of concern, that is effects on the developing fetus, thus necessitating the use of an oral study for risk assessment.

Due to the very low oral absorption of DDAC as demonstrated by the available toxicokinetic study, the oral NOAEL of 1 mg/kg bw/day, which represents an externally administered dose level, was adjusted to 0.05 mg/kg bw/day to correct for an approximate oral absorption estimation of 5% to allow for extrapolation to systemic exposure estimates via the dermal route of exposure.

The target margin of exposure (MOE) selected for this endpoint is 100. Tenfold factors were applied each for interspecies extrapolation and intraspecies variability. For residential scenarios, the PCPA factor was reduced to onefold as outlined in the *Pest Control Products Act* hazard characterization Section.

The selection of this study and target MOE is considered to be protective for youth and adults, including the unborn children of exposed women. It provides margins of 30,000 or higher to dose levels shown to cause effects on fertility or fetal development in mice in the literature, and a margin of 6000 to the point of departure for the increased fetal mortality observed in the presence of maternal toxicity in the guideline rabbit developmental toxicity study.

**Long-term dermal – children (1-11 years old) (residential)**

For the long-term dermal risk assessments for children, the NOAEL of 12 mg/kg bw/day from the 90-day dermal toxicity study in rats was selected, which was the highest dose level tested in this study. No systemic toxicity was observed up to the highest dose tested in this study; however, severe dermal irritation was noted at all dose levels. This study was conducted via the relevant route of exposure. The endpoints of delayed ossification and increased variations that were observed in the rat and rabbit developmental toxicity studies are only relevant to sub-populations that may include women of reproductive age, and are therefore not relevant to this sub-population.

The target MOE is 100, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. Since evidence of systemic toxicity following dermal application is lacking and irritation is the primary effect noted after repeated dermal dosing, it is unlikely that dosing over a longer interval would produce a significantly different result than that noted in the 90-day study; as such, an additional uncertainty factor for extrapolation from a short-term study to a long-term exposure scenario is not warranted. The PCPA factor was reduced to onefold as discussed in the *Pest Control Products Act* hazard characterization Section.

The endpoints of delayed ossification and variations observed in fetuses in the developmental toxicity studies are not relevant to this sub-population. Therefore, the selection of this study and target MOE is considered to be protective for children.

**Long-term inhalation – adults (greater than 16 years old) and youth (11-16 years old) (occupational and residential)**

For the long-term inhalation risk assessments for adults and youth, the lowest observed adverse effect concentration (LOAEC) of 0.091 mg/m$^3$ (equivalent to a lowest observed adverse effect level (LOAEL) of 0.02 mg/kg bw/day) from the 28-day inhalation toxicity study in rats was selected. At the LOAEC, which was the lowest concentration tested, evidence of respiratory tract irritation and inflammation was observed. This study was conducted via the relevant route of exposure.

The target MOE selected for this endpoint for long-term scenarios is 1000. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. An additional threefold uncertainty factor was applied to account for the use of a LOAEL, and an additional threefold uncertainty factor was applied to account for potential increased toxicity with increased duration of exposure for portal of entry effects since a long-term inhalation study was not available. For residential scenarios, the PCPA factor was reduced to onefold as outlined in the *Pest Control Products Act* hazard characterization Section.

The selection of this study and target MOE provides a margin of 50 000 to the developmental NOAEL in rats and rabbits, and margins of 375 000 or higher to dose levels shown to cause effects on fertility or fetal development in mice in the literature, and is therefore considered to be protective for all populations, including the unborn children of exposed women.

**Long-term incidental oral – children (1-2 years old) (residential)**

For long-term incidental oral risk assessments for children, the maternal NOAEL of 1 mg/kg bw/day from the oral developmental toxicity studies in rats and rabbits was selected. At dose levels of 10 mg/kg bw/day in the rat and 3 mg/kg bw/day in the rabbit, clinical signs of toxicity, such as audible respiratory and hypoactivity, were noted. This study provides the lowest point of departure in studies conducted via the relevant route of exposure. Additionally, the observed effects are not specific to adult or maternal animals and are considered relevant for children.

The target margin of exposure (MOE) is 100, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The PCPA factor was reduced to onefold as discussed in the *Pest Control Products Act* hazard characterization Section. The endpoints of delayed ossification and variations observed in fetuses in the developmental toxicity studies are not relevant to this sub-population. Therefore, the selection of this study and target MOE is considered to be protective for children.

**Dermal sensitization**

Because of the positive skin sensitization study findings and the proposed use pattern for DDAC, a quantitative dermal sensitization risk assessment was deemed appropriate. An $EC_3$ value of 0.17%, equivalent to 42.5 µg/cm$^2$, was established as a threshold for induction in the local lymph node assay (LLNA) study in the published scientific literature and was considered appropriate for use in the risk assessment. The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability.

### 3.2.3 Acute reference dose (ARfD)

Establishment of an acute reference dose is not required, as no exposure via the diet or drinking water is expected.

### 3.2.4 Acceptable daily intake (ADI)

Establishment of an acceptable daily intake is not required, as no exposure via the diet or drinking water is expected.

### 3.2.5 Cancer assessment

There was no evidence of tumourigenicity and therefore, a cancer risk assessment is not necessary.

## 3.3 Aggregate toxicology reference values

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). Long-term aggregate exposure to DDAC may be composed of residential exposure of adults via the dermal (wearing laundered clothing) and inhalation (open pour of laundry detergent) routes, and of children via the incidental oral (mouthing laundered clothing) and dermal (wearing laundered clothing) routes.

For adults, the toxicology endpoint selected for aggregation was delayed ossification and variations in the developing fetus. For the dermal and inhalation routes, the adjusted developmental NOAEL of 0.05 mg/kg bw/day from the oral rat and rabbit developmental toxicity studies was selected with a target MOE of 100. The PCPA factor for all routes was onefold as set out in the *Pest Control Products Act* hazard characterization Section.

For children, no endpoints were selected for long-term aggregate risk assessment as no effect common to the oral and dermal routes was identified. The endpoint relevant to the oral route was generalized toxicity (clinical signs in maternal animals in the developmental toxicity studies) whereas no systemic toxicity endpoint was observed in the 90-day dermal toxicity study in rats.

## 3.4 Occupational and residential risk assessment

### 3.4.1 Dermal absorption

A chemical-specific dermal absorption study was not submitted and is not on file for DDAC. The dermal reference values for adults and youth were based on rat and rabbit oral developmental toxicity studies (co-critical). Therefore, a standard dermal absorption value of 100% was used for the dermal risk assessment for adults and youth. For children, a dermal absorption factor is not required since the dermal reference value is based on a dermal toxicology study.

### 3.4.2 Occupational exposure and risk

#### 3.4.2.1 Mixer/loader exposure and risk assessment

There is potential for exposure to workers mixing/loading Acticide DDQ 50-E. Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted. Therefore, dermal and inhalation exposure estimates for workers mixing/loading Acticide DDQ 50-E in manufacturing facilities were generated using the Antimicrobial Exposure Assessment Task Force II (AEATF II) database for liquid open-pour scenario. Exposure to workers mixing/loading Acticide DDQ 50-E is expected to be long term in duration and to occur primarily by the dermal and inhalation routes. The exposure estimates are based on mixers/loaders wearing single layer and chemical-resistant gloves.

Dermal and inhalation exposures were estimated by coupling the maximum application rate and the amount of product handled per day with the unit exposure values from the AEATF II liquid-pour study and 100% absorption for both routes. The average amount of Acticide DDQ 50-E handled per day by a worker, manually adding the preservative to the polymer dispersions, lattices, solutions, resins, and biopolymers, was reported to be 3 kg. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological reference values (NOAELs for dermal and LOAEC for inhalation) to obtain the MOE; the target MOE is 100 for dermal exposure and 1000 for inhalation exposure. Calculated dermal and inhalation MOEs for the open pouring of Acticide DDQ 50-E exceeded the target MOEs (Table 1), therefore, there are no health risks of concern.

**Table 1 Mixer/Loader risk assessment for DDAC using liquid open pour**

| Scenario | Use | Application rate[a] (g a.i/L) | Amount handled per day[b] (g a.i/day) | Unit exposure value[c] (µg/kg a.i) | | Daily exposure[d] (mg/kg bw/day) | | MOE[e] | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Dermal | Inhalation | Dermal | Inhalation | Dermal | Inhalation |
| **PPE: Single layer, chemical-resistant gloves** | | | | | | | | | |
| Liquid open pour | Polymer dispersions, lattices, solutions, resins, and biopolymers intended for use in industrial and household/institutional laundry detergents | 1.00 | 3.226 | 2135.38 | 5.08 | 0.0001 | 0.0000002 | 581 | 9.76E+04 |

a.i. – active ingredient; MOE – margin of exposure

[a] Maximum rate for DDAC

[b] Amount handled per day: Application rate × [Amount of end-use product handled per day (3 kg, provided by applicant) / Density of the end-use product (0.93 kg/L )]
[c] Unit exposure values from AEATF II Liquid open pour studies
[d] Daily exposure = [Amount handled per day × Unit exposure value × Absorption (100% for dermal and inhalation) × Certainty Factor 1 (1 mg/1000 µg) × Certainty Factor 2 (1 kg/1000 g)] /80 kg bw
[e] MOE = NOAEL/Exposure; Target MOE = 100 for long-term dermal (NOAEL = 0.05 mg/kg bw/day); MOE = 1000 for long-term inhalation (LOAEC = 0.02 mg/kg bw/day)

#### 3.4.2.2 Postapplication worker exposure and risk

There is potential for exposure to workers entering facilities where polymers treated with Acticide DDQ 50-E are manufactured. In addition, for preserved polymers intended for use in industrial and household/institutional laundry detergents, there is potential for exposure to secondary workers handling laundry detergents in commercial (large or small scale) laundry service facilities (for example, handling laundry from hotels, hospitals, restaurants).

##### 3.4.2.2.1 Postapplication worker exposure in manufacturing facilities

For postapplication exposure to workers in facilities where polymers treated with Acticide DDQ 50-E are manufactured, there is potential for dermal exposure to downstream workers in the facilities. Since these workers are expected to be wearing personal protective equipment as specified in the regulations regarding worker health and safety, it is expected that this will limit potential exposure when conducting postapplication activities.

##### 3.4.2.2.2 Secondary worker exposure

For polymers intended for use in industrial and household/institutional laundry detergents, there is potential for exposure to secondary workers handling these preserved laundry detergents in commercial (large or small scale) laundry service facilities (for example, handling laundry from hotels, hospitals, restaurants). The typical concentration of Acticide DDQ 50-E in a laundry detergent was calculated as 0.0005 kg per 1000 kg detergent. The typical usage level of a detergent in laundry facilities is provided in Table 2. However, as the source of the information was not provided, there is some uncertainty associated with these levels, therefore, the most conservative value of 101.9 kg/day was used in the risk assessment.

**Table 2 Typical usage level of a detergent at laundry facilities**

| Facility type | Light soil product usage total (kg/day) | Heavy soil product usage total (kg/day) | Estimated total detergent usage (kg/day) |
|---|---|---|---|
| Small healthcare/motel | 1.1 | 3.4 | 2.6 |
| Medium Healthcare/Hotel | 2.8 | 8.5 | 6.5 |
| Large Hotel/Resort/Hospital | 8.5 | 25.5 | 19.6 |
| Industrial Laundry | 34.0 | 101.9 | 78.4 |

Dermal and inhalation unit exposure values were obtained from the AEATF II liquid open-pour studies, where short-sleeved shirt, shorts, no gloves, and no respirator unit exposure values were used as a surrogate for the "single layer, no gloves" clothing level. For body weight, 80 kg was used. For amount handled per day, when using a worst-case scenario of 101.9 kg/day of laundry detergent for heavily soiled products, and a concentration of 0.0005 kg of Acticide DDQ 50-E per 1000 kg detergent, this is equivalent to 0.0000005 kg Acticide DDQ 50-E * 50% Guarantee = 0.00000025 kg a.i in 1 kg laundry detergent.

Using this concentration and the maximum amount of laundry detergent handled per day, the calculated dermal and inhalation MOEs exceeded the target MOE (Table 3), therefore, there are no health risks of concern.

**Table 3 Secondary worker exposure and risk assessment for DDAC using liquid open pour**

| Scenario | Use | Concentration of DDAC in laundry detergent (kg a.i/kg) | Amt handled per day[a] (kg a.i/day) | Unit exposure value[b] (µg/kg a.i) | | Daily Exposure[c] (mg/kg bw/day) | | MOE[d] | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Dermal | Inhalation | Dermal | Inhalation | Dermal | Inhalation |
| **PPE:** short-sleeved shirt, shorts, no glove | | | | | | | | | |
| Liquid open pour | Laundry detergent | 2.50E-07 | 2.55E-05 | 22, 042.37 | 5.08 | 7.02E-06 | 1.62E-09 | 7.12E+03 | 1.24E+07 |

[a] Amount handled per day (kg a.i/day) = 101.9 kg detergent per day * Concentration of DDAC in detergent.
[b] Unit exposure values from AEATF II Liquid open pour studies
[c] Daily exposure = [Amount handled per day × Unit exposure value × Absorption (100% for dermal and inhalation) × Certainty Factor (1 mg/1000 µg)] /80 kg bw
[d] MOE = NOAEL/Exposure; Target MOE = 100 for long-term dermal (NOAEL = 0.05 mg/kg bw/day); MOE = 1000 for long-term inhalation (LOAEC = 0.02 mg/kg bw/day)

### 3.4.3 Residential exposure and risk assessment

There is potential for dermal and inhalation exposure to occur for residential handlers adding laundry detergent to laundry, and for dermal exposure to adults, youth, and children wearing clothing laundered with laundry detergent containing DDAC. In addition, incidental oral exposure for children (1 to <2 years old) to DDAC residues on laundered clothing may occur. Given that the product will be used on a routine basis year-round, it is expected that exposure will be long term in duration. It is assumed that most ingredients in laundry detergents are water soluble. Water-soluble laundry detergents do not bind to treated clothing and are rinsed away during the wash cycle, thus minimizing the amount of residue available for exposure. Since DDAC is water soluble, it is expected that the amount of DDAC residues available for exposure will be reduced following washing. This is reflected in the standard weight fraction of detergent deposited on fabric (5%) used in the exposure equations.

### 3.4.3.1 Handler exposure and risk

A risk assessment was conducted to assess dermal and inhalation exposure when residential handlers are adding laundry detergent to the washing machine. The amount handled per day for residential handlers was obtained from the USEPA Antimicrobial Division Residential SOPs. Dermal and inhalation unit exposure values were obtained from the AEATF II liquid open-pour studies. The standard amount of product handled per day for liquid laundry additives (920 g product/day; 0.92 kg product/day) is based on the amount of product added per load (230 g/load) and the number of laundry events (load) per day (4 events). Body weight used was 80 kg. The typical concentration of Acticide DDQ 50-E in a laundry detergent was reported to be 0.0005 kg per 1000 kg detergent or 0.00000025 kg a.i in 1 kg laundry detergent.

Calculated dermal and inhalation MOEs exceeded the target MOEs (Table 4), therefore, there are no health risks of concern.

**Table 4 Residential handler exposure to DDAC in laundry detergent using liquid open-pour**

| Scenario | Use | Concentration of DDAC in laundry detergent (kg a.i./kg) | Amount handled per day[a] (kg a.i./ day) | Unit exposure value[b] (µg/kg a.i) | | Daily Exposure[c] (mg/kg bw/day) | | MOE[d] | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Dermal | Inhalation | Dermal | Inhalation | Dermal | Inhalation |
| **PPE: Short-sleeved shirt and shorts only** | | | | | | | | | |
| Liquid open pour | Laundry detergent | 2.50E-07 | 2.30E-07 | 22,042.37 | 5.08 | 6.34E-08 | 1.46E-11 | 7.89E+05 | 1.37E+09 |

[a] Amount handled per day: USEPA Antimicrobial Division Residential SOP; amount of product (detergent) added per load (230 g/load) and the number of laundry events (load) per day (4).
[b] Unit exposure values from AEATF II Liquid open pour studies
[c] Daily exposure = [Amount handled per day × Unit exposure value × Absorption (100% for dermal and inhalation) × Certainty Factor (1 mg/1000 µg)] /80 kg bw
[d] MOE = NOAEL/Exposure; Target MOE = 100 for long-term dermal (NOAEL = 0.05 mg/kg bw/day); MOE = 1000 for long-term inhalation (LOAEC = 0.02 mg/kg bw/day)

### 3.4.3.2 Postapplication exposure and risk

**Dermal exposure to laundered clothing**

Exposure to preservative residues in laundered clothing is outlined in the Antimicrobial Division Residential SOP for dermal exposure to adults and children (1 to < 2 years old). The dermal systemic risk assessment was based on the following equation and the standards from the SOP:

$$D = (((M \times F1 \times DF \times F') / WI) \times (SA \times F2 \times F3 \times DAF)) / BW$$

Where:
D = Daily exposure (mg/kg/day)
M = Amount of undiluted product used (230 000 mg)
F1 = Weight fraction of a.i in product (2.5E-07%)
DF = Density of fabric (20 mg/cm$^2$; cotton, chosen to cover all fabric types)
F' = Weight fraction of detergent deposited on fabric (5%)
WI = Total weight of fabric (1 kg = 1 000 000 mg)
SA = Body surface area contacting clothing (cm$^2$/day), entire body minus the head
F2 = Weight fraction transferred from clothing to skin (100%)
F3= Weight fraction remaining on skin (100%)
DAF = Dermal absorption factor (100%)
BW = Body weight (kg)

Calculated MOEs exceeded the target MOE of 100 (Table 5), therefore, there are no health risks of concern.

**Table 5 Residential dermal exposure to laundered clothing (Adult, Youth, Children)**

| Scenario | Use | Amount of undiluted product used (M), mg | Fraction of a.i in product (F1) % a.i.[a] | Density of Fabric (D) (mg/cm$^2$) [b] | Weight Fraction of detergent deposited on fabric (F') % | Total weight of fabric (WI) mg | Weight fraction transferred from clothing to skin (F2) % | Weight fraction remaining on skin (F3) % | Potential Exposure mg/cm$_2$ | Daily Exposure[c] (mg/kg/day) | MOE[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Adult | Laundry detergent | 230 000 | 2.5E-07 | 20 | 0.05 | 1000000 | 1 | 1 | 1.05E-03 | 1.31E-05 | 3.81+03 |
| Youth | Laundry detergent | 230 000 | 2.5E-07 | 20 | 0.05 | 1000000 | 1 | 1 | 8.72E-04 | 1.53E-05 | 3.27E+03 |
| Children (1 to <2 years old) | Laundry detergent | 230 000 | 2.5E-07 | 20 | 0.05 | 1000000 | 1 | 1 | 2.54E-04 | 2.31E-05 | 5.19E+05 |

[a] Weight fraction of a.i. in product
[b] Pure cotton fabric was chosen as the most conservative to represent all fabric types.
[c] Daily Exposure (mg/kg bw/day) = [(Product used (mg) × a.i in product (%) × density of fabric (mg/cm$^2$) x detergent deposited (%)/weight of fabric (mg)) × body surface area (cm$^2$) × fraction transferred (%) × fraction on skin (%)] / body weight (kg; 11 kg for toddlers, 80 kg for adults, 57 kg for youth)
[d] Long-term exposure based on a dermal NOAEL = 0.05 mg/kg bw/day for adults, youth; NOAEL = 12 mg/kg bw/day; MOE = 100 for adults, youth and children
Surface area of entire body minus the head: adult = 18250 cm$^2$/day; youth = 15 169 cm$^2$/day; children (1 to <2 years old) = 4425 cm$^2$/day; Calculated based on body surface area values from SPN2014-01 (page 9; Table 3.3.1), and percent surface area of body parts from Exposure Factor Handbook (2011; page 15, Table ES-1)

## Incidental oral exposure to laundry detergent preservatives

Incidental oral exposure to DDAC from mouthing laundered clothing was calculated using standard assumptions from the Antimicrobial Division Residential SOP. As stated above for dermal exposure, the density of cotton fabric was chosen for the risk assessment to cover all other fabric types. This was based on the equation:

PDD = (((M × F1 × DF × F') / WI) × (SA × SE)) / BW

Where:
PDD = Potential daily dose (mg/kg/day)
M = Amount of undiluted product used (230 000 mg)
F1 = Weight fraction of a.i in product (2.5E-07%)
DF = Density of fabric (20 mg/$cm^2$)
F' = Weight fraction of detergent deposited on fabric (5%)
WI = Total weight of fabric (1 000 000 mg)
SA = Surface area of fabric mouthed (50 $cm^2$/day)
SE = Saliva extraction efficiency (48%)
BW = Body weight (kg)

Calculated MOE exceeded the target MOE of 100 (Table 6), therefore, there are no health risks of concern.

**Table 6 Incidental oral exposure to laundered clothing (Children 1 to <2 years old)**

| Scenario | Use | Amount of undiluted product used (M), mg | Weight fraction of a.i in product (F1) % a.i[a] | Fabric Density (D) (mg/$cm^2$)[b] | Weight Fraction of detergent deposited on fabric (F') %/100 | Total weight of fabric (WI) mg | Surface area of fabric mouthed (SA) $cm^2$/day | Saliva extraction efficiency (SE) %/100 | Body weight (BW) kg | Potential Daily Dose[c] (PDD) mg/kg/day | MOE[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Children (1 to <2 years old) | Laundry detergent | 230 000 | 2.5E-07 | 20 | 0.05 | 1 000 000 | 50 | 0.48 | 11 | 1.25E-07 | 7.97E+06 |

[a] Weight fraction of a.i in product
[b] Pure cotton fabric was chosen as the most conservative to represent all fabric types.
[c] Potential daily dose (mg/kg bw/day) = [(Product used (mg) × a.i in product (%) × density of fabric (mg/$cm^2$) × detergent deposited (%)/weight of fabric (mg)) × surface area of fabric mouthed ($cm^2$/day) × saliva extraction efficiency (%)] / body weight (kg; 11 kg for toddlers)
[d] MOE = NOAEL/Exposure; Target MOE = 100 for incidental oral exposure.
NOAEL incidental oral = 1 mg/kg bw/day

## Dermal sensitization risk assessment

As Acticide DDQ 50-E is considered a potential dermal sensitizer, a dermal sensitization risk assessment was conducted. For dermal sensitization to be considered acceptable, dermal exposure from Acticide DDQ 50-E must fall below the threshold for dermal sensitization. Dermal sensitization is expected to occur through short-term duration contact scenarios. A single contact event has the potential to cause dermal sensitization.

The film thickness approach described in the Exposure Factors Handbook was used to estimate dermal sensitization. This approach was based on experiments conducted to estimate the retention of six different types of liquids on hands following contact under five different exposure conditions. The liquids were selected based on their non-toxic characteristics and the

fact that they represented a range of viscosities and likely retention of residues on the hands. These liquids included mineral oil, cooking oil, water-soluble bath oil, 50:50 oil/water emulsion, water, and 50:50 water/ethanol. The five exposure conditions used to simulate activities in which consumers' hands may be exposed to liquids included contact with dry skin (initial contact), contact with skin previously exposed to the liquid and still wet (secondary contact), immersion of a hand into a liquid, contact from handling a wet rag, and contact during spill clean-up. The first exposure condition (initial contact) involved rubbing a cloth saturated with liquid over the front and back of both clean, dry hands for the first time during an exposure event. The secondary contact scenario involved rubbing a cloth saturated with liquid over the front and back of both hands for a second time, after which a clean cloth was used to thoroughly remove the liquid that adhered to skin during the first contact event. In the immersion scenario, one hand was immersed in a container of liquid and then removed, then the liquid was allowed to drip back into the container for 30 seconds (60 seconds for cooking oil). For the scenario involving contact from handling a wet rag, a cloth saturated with liquid was rubbed over the palms of both hands. For the scenario involving spill clean-up, exposure was simulated by using a clean cloth to wipe up 50 mL of liquid poured onto a plastic laminate countertop. For each of these scenarios, retention was measured immediately after the activity was completed by measuring the liquid amount lost from either the saturated cloth or the immersing liquid. Film thickness (cm) was estimated as the amount of liquid retained on the skin ($g/cm^2$) divided by the density of the liquid ($g/cm^3$) used in the experiment. A limitation of the study is the fact that only six liquid formulations were tested and none were specific to treated products such as laundered clothing.

The exposure condition involving immersion of hands into a liquid with no wipes and for a mineral oil formulation was considered representative of DDAC residues deposited/retained on the skin from handling laundry detergent preserved with DDAC. It is assumed that dermal contact occurs by immersion of hands into an undiluted liquid detergent. This is likely an over-estimation since most detergents where workers or homeowners immerse their hands are diluted. Exposure is calculated using film thickness data together with the density of the liquid and the weight fraction of the chemical in the liquid.

In addition, there is the potential for dermal sensitization to occur for adults and children from wearing clothing laundered with the detergent. Both dermal sensitization from handling laundry detergent and from wearing clothing laundered with the detergent were assessed.

**Table 7 Dermal sensitization risk assessment**

| Use scenario | Weight fraction for end-use product[a] | Film thickness (cm)[b] | Density ($g/cm^3$)[c] | Exposure[d] ($\mu g/cm^2$) | $EC_3$ ($\mu g/cm^2$) | MOE[e] |
|---|---|---|---|---|---|---|
| Handling laundry detergent (for example, hand washing) | 0.0000005 | 0.01187 | 0.872 | 0.00518 | 42.5 | 8212 |

[a] Weight Fraction (unitless): The typical concentration of Acticide DDQ 50-E in a laundry detergent is calculated as 0.0005 kg per 1000 kg detergent = 0.0005 kg end-use product/1000 kg detergent = 0.0000005
[b] Film thickness for immersion of hands into a liquid with no wipes/mineral oil formulation (cm) = $11.87 \times 10^{-3}$ (Exposure Factors Handbook; Table 7–24)
[c] Mineral oil density ($g/cm^3$) = 0.872 (Exposure Factors Handbook; Table 7–24)
[d] Exposure ($\mu g/cm^2$) = Weight fraction of end-use product (unitless) × Film thickness (cm) × mineral oil density ($g/cm^3$) × Certainty Factor (1 000 000 µg/1g)
[e] MOE = $EC_3$/Exposure, Target MOE = 100; $EC_3$ = 42.5 $\mu g/cm^2$

When wearing clothes laundered with the detergent, the calculated MOE exceeded the target MOE for dermal sensitization, therefore, there are no health risks of concern.

**Table 8 Residential exposure to laundered clothing (Adult, youth, children) - Sensitization effects**

| Scenario | Use | Amount of undiluted product used (M), mg | Weight fraction of a.i in product (F1) % a.i[a] | Density of Fabric (DF) ($mg/cm^2$) [b] | Weight Fraction of detergent deposited on fabric (F') %/100 | Total weight of fabric (WI) mg | Weight fraction transferred from clothing to skin (F3) %/100 | Weight fraction rem. on skin (F2) %/100 | Dermal Loading (µg/cm) [c] | MOE[d] |
|---|---|---|---|---|---|---|---|---|---|---|
| Wearing clothing laundered with an antimicrobial-preserved product (adults, youth, children) | Laundry detergent | 230 000 | 2.5E-07 | 20 | 0.05 | 1000000 | 1 | 1 | 5.75E-05 | 7.39E+05 |

[a] Weight fraction of a.i in product = The typical concentration of Acticide DDQ 50-E in a laundry detergent is calculated as 0.0005 kg per 1000 kg detergent = 0.0005 kg end-use product/1000 kg detergent = 0.0000005
[b] Pure cotton fabric was chosen as the most conservative to represent all fabric types..
[c] Dermal Loading ($ug/cm^2$) = [(Amount of undiluted product used (mg) × weight fraction of a.i in product (% a.i/100) × density of fabric ($mg/cm^2$) × weight fraction of detergent deposited on fabric (%/100) / Total weight of fabric (mg)) × fraction transferred from clothing to skin (%) × weight fraction remaining on skin (%/100) × Certainty Factor (1000 µg/mg]
[d] MOE = $EC_3$/Exposure, Target MOE = 100; $EC_3$ = 42.5 $\mu g/cm^2$

### 3.4.3.3 Aggregate exposure and risk assessment

Aggregate risks were estimated for exposure to laundry detergent preservatives for adults via the dermal and inhalation routes when handling laundry detergent and dermal route when wearing laundered clothing (Table 9). Given that no reference value common to the oral and dermal routes was identified for children 1–2 years old, an aggregate assessment for this sub-population is not required.

Calculated MOE exceeded the target MOE of 100 (Table 9), therefore, there are no health risks of concern for adult aggregate exposure to DDAC.

**Table 9 Adult aggregate exposure to DDAC**

| Scenario | Exposure route | Exposure (mg/kg bw/day) | Aggregate exposure (mg/kg bw/day) | MOE |
|---|---|---|---|---|
| Laundry detergent preservatives – Liquid open pour | Dermal[1] | 6.34E-08 | 1.32E-05 | 3793 |
| | Inhalation[1] | 1.46E-11 | | |
| Laundry detergent preservatives – Wearing laundered clothing – Adult | Dermal[2] | 1.31E-05 | | |

[1]Exposure obtained from Table 4
[2]Exposure obtained from Table 5
NOAEL (dermal and inhalation) = 0.05 mg/kg bw/day; Target MOE = 100

#### 3.4.3.4 Bystander exposure and risk

Bystander exposure is expected to be negligible for industrial scenarios where Acticide DDQ 50-E is used in the manufacturing of the laundry detergent.

### 3.5 Health incident reports

As of 20 March 2024, 10 human incident reports involving DDAC were submitted to the PMRA.

All human incidents were considered possibly related to the reported DDAC product. People were exposed to DDAC in both occupational as well as non-occupational settings. Reported exposure scenarios in occupational settings included, coming in contact with treated lumber, disinfecting/cleaning surfaces with DDAC disinfectants, or coming in contact with a technical grade product as a result of equipment failure. Exposure in non-occupational settings mainly occurred at residential sites. People (includes 2 children) reported exposure either as a result of walking or sleeping in areas treated with a DDAC disinfectant or following application of a DDAC disinfectant product to furniture in living areas.

The severity of effects reported in people were mainly minor. Reported effects frequently included skin irritation/rash, eye irritation or cough. In one major Canadian incident, an individual reported experiencing hives, shortness of breath, chest tightness, respiratory irritation, itchy skin and rash, following application of a domestic class DDAC product in her living area. This domestic class product is no longer registered in Canada.

Overall, the review of human incidents involving DDAC indicates a potential for adverse effects in people, either via the dermal, ocular, or respiratory route, when using/applying DDAC

products or when coming into contact with areas that have been treated with DDAC. The label of the product, Acticide DDQ 50-E, contains appropriate signal words, personal protective equipment, and precautionary statements to minimize dermal, ocular, or inhalation exposure in workers during use of the product. Therefore, no additional mitigation measures are being proposed as a result of this incident report review.

### 3.6 Cumulative assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for DDAC. DDAC belongs to the quaternary ammonium compound class of antimicrobials, which is a group of biocides that consists of the DDAC cluster, the ADBAC cluster, and other related compounds. In general, quaternary ammonium biocides are reactive chemicals and as such, cause point of contact adverse effects such as irritation or corrosion of the skin and eyes, irritation of the respiratory tract, and irritation-type responses of the gastrointestinal tract. These effects are non-specific and a common mechanism of toxicity has not been identified. Therefore, no cumulative health risk assessment is required at this time.

## 4.0 Impact on the environment

### 4.1 Fate and behaviour in the environment

DDAC is hydrolytically stable under abiotic and buffered solutions over the pH 5–9 range. It is also stable to photodegradation in pH 7 buffered aqueous solution. Even in the presence of a photosensitizer (acetone), DDAC degradation is minimal. DDAC is also photolytically stable in soil.

DDAC is stable to microbial degradation in aquatic systems and in aerobic soils. It is immobile in soil and has a strong tendency to bind to sediment/soil. Because of this, DDAC is not expected to contaminate surface and ground waters. Hence, bioconcentration of DDAC in aquatic organisms is not likely to occur.

The environmental fate and behaviour of DDAC was previously published under Proposed Re-evaluation Decision PRVD2008-27 and Re-evaluation Decision RVD2009-07, *Didecyl Dimethyl Ammonium Chloride Cluster (DDAC)* and also, PRVD2016-24 and RVD2017-09, *Antisapstain and Joinery Uses of Didecyl Dimethyl Ammonium Chloride (DDAC)*.

### 4.2 Environmental risk characterization

Acticide DDQ 50-E is to be added to the polymer material during the manufacturing process to provide long-term antimicrobial protection during transportation and bulk storage, at rates between 0.02% and 0.2% by weight (100 to 1000 ppm DDAC). This proposed use of DDAC results in minimal exposure and risk to non-target organisms in the environment.

Thus, environmental exposure to DDAC from the proposed use of Acticide DDQ 50-E is not expected to exceed existing levels. The risk to the environment is expected to remain acceptable and a quantitative environmental risk assessment was not conducted.

### 4.2.1 Risks to terrestrial and aquatic organisms

**Effects on non-target terrestrial organisms:**
With the proposed use pattern and application method, data on the toxic effects of DDAC to terrestrial organisms is not required, as exposure to terrestrial organisms is not expected.

**Effects on aquatic organisms:**
Existing information and reviews based on several registered use patterns (use-site categories: 2, 3, 5, 6, 15, 17, 19, and 23) have indicated that DDAC is highly toxic to very highly toxic to aquatic organisms. Refer to PRVD2008-27 and PRVD2016-24 for further details.

With the proposed use pattern and application method, data on the toxic effects of DDAC to aquatic organisms is not required, as exposure to aquatic organisms is not expected.

Based on the use pattern and limited exposure potential, terrestrial and aquatic environmental risk is expected to be acceptable for this proposed major new use.

### 4.3 Incident reports

As of 20 March 2024, no environmental incidents involving DDAC have been reported to the PMRA.

## 5.0 Value

Bacterial and fungal contamination of materials during the manufacturing process is very difficult to prevent. Aqueous polymer emulsions contain the water, organic compounds, and micronutrients needed by microorganisms to multiply. Even with intensive cleaning and biocontrol practices, microbial contamination still occurs. If bacteria and fungi grow unchecked, they can spoil the polymer material and make it unsuitable for use in downstream applications (such as a component of laundry detergents). Material preservatives kill and/or slow the growth of bacteria and fungi that may be introduced during manufacturing.

Laboratory efficacy trials tested Acticide DDQ 50-E's ability to kill bacteria, yeast, and mould in polymers. Three different polymer materials were treated with a range of concentrations of Acticide DDQ 50-E. The test replicates were inoculated with mixed cultures of bacteria or fungi (yeast and mould), then incubated to encourage microbial growth. Samples were streaked onto solid agar plates, which were later examined for growth, and scored following a qualitative rating scale. The process of adding bacterial or fungal culture, incubating, and streaking samples onto agar plates was repeated multiple times on each replicate to evaluate Acticide DDQ 50-E's ability to protect materials from ongoing, repeated contamination events that may occur during the manufacturing, transportation, and storage lifecycle of the product.

The effectiveness of Acticide DDQ 50-E was determined by comparing the amount of growth in treated samples with the growth in untreated samples. The results of this study demonstrated Acticide DDQ 50-E is effective when added at rates between 0.02% and 0.2% by weight.

The registrant reported that there are no known non-safety adverse effects associated with using Acticide DDQ 50-E to preserve polymer emulsions and dispersions.

# 6.0 Pest control product policy considerations

## 6.1 Assessment of the Active Ingredient under the Toxic substances Management Policy

The PMRA has reached the conclusion that technical grade DDAC and its transformation products do not meet the Toxic Substances Management Policy (TSMP) Track 1 criteria. Further details on the original TSMP assessment can be found in PRVD2008-27 and PRVD2016-24.

## 6.2 Formulants and Contaminants of Health or Environmental Concern

There are no formulation changes proposed under the current submissions. Acticide DDQ 80-F and its end-use product do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Environmental Concern*. Thus, there are no new concerns under the Pest Control Product Policy.

# 7.0 Summary

## 7.1 Human health and safety

Mixers and loaders handling Acticide DDQ 50-E and workers handling laundry detergents in industrial laundry service facilities, are not expected to be exposed to levels of DDAC that will result in an unacceptable risk when DDAC is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

Residential exposure to individuals handling laundry detergent, and wearing clothing laundered with the detergent is not expected to result in unacceptable risk when DDAC is used according to label directions.

## 7.2 Environmental risk

DDAC is not expected to build-up in the environment, and exposure to non-target organisms is expected to be low. Under the use pattern proposed, DDAC is not expected to present a risk to non-target terrestrial and aquatic organisms. When used as a material preservative in accordance with the label directions and the required precautions, the product Acticide DDQ 50-E is expected to pose acceptable risks to the environment.

### 7.3 Value

The data submitted to register the DDAC-containing product Acticide DDQ 50-E was sufficient to support its efficacy as an in-can preservative of synthetic and naturally-derived polymer emulsions and dispersions. Acticide DDQ 50-E will provide manufacturers an alternative in-can preservative that may help address issues with material compatibility, cost, microbial resistance or active ingredient availability.

## 8.0 Proposed regulatory decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Acticide DDQ 80-F and Acticide DDQ 50-E, containing the technical grade active ingredient DDAC, for use as a material preservative in polymers.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

# List of abbreviations

| | |
|---|---|
| ↑ | increased |
| ↓ | decreased |
| ♀ | female |
| ♂ | male |
| µg | microgram |
| µM | micromolar |
| °C | degrees centigrade |
| a.i. | active ingredient |
| abs. | absolute |
| AD | administered dose |
| ADBAC | alkyl dimethyl benzyl ammonium chloride |
| ADD | absorbed daily dose |
| ADI | acceptable daily intake |
| AEATF | Antimicrobial Exposure Assessment Task Force II |
| ALS | acetolactate synthase |
| ARfD | acute reference dose |
| atm | atmosphere |
| BALF | bronchoalveolar lavage fluid |
| bw | body weight |
| bwg | body weight gain |
| CAS | Chemical Abstracts Service |
| cm | centimetres |
| $cm^2$ | square centimetre(s) |
| DDAC | Didecyl Dimethyl Ammonium Chloride |
| DEEM | Dietary Exposure Evaluation Model |
| DER | data evaluation report |
| DF | dry flowable |
| DNA | deoxyribonucleic acid |
| DPRA | Direct Peptide Reactivity Assay |
| $EC_3$ | concentration required to induce a threshold positive sensitization response |
| $F_1$ | first filial generation |
| $F_2$ | second filial generationg gram |
| GD | gestation day |
| GIT | gastrointestinal tract |
| GAP | Good Agricultural Practice |
| ICOS | inducible T-cell costimulator |
| IgE | immunoglobulin E |
| IL | interleukin |
| ILC | innate lymphoid cell |
| h-CLAT | human Cell Line Activation Test |
| ha | hectare |
| HCT | hematocrit |
| HGB | hemoglobin |
| hr | hour |

| | |
|---|---|
| kg | kilogram |
| KLRG1 | killer cell lectin-like receptor G1 |
| km | kilometre |
| L | litre |
| $LD_{50}$ | lethal dose 50% |
| LDH | lactate dehydrogenase |
| LLNA | local lymph node assay |
| LOAEL | lowest observed adverse effect level |
| LOAEC | low observed adverse effect concentration |
| m | metre |
| $m^3$ | cubic metre(s) |
| mg | milligram |
| mL | millilitre |
| mm | millimetre |
| MOE | margin of exposure |
| mRNA | messenger ribonucleic acid |
| NIOSH | National Institute for Occupational Safety and Health |
| NOAEC | no observed adverse effect concentration |
| NOAEL | no observed adverse effect level |
| NTD | neural tube defect |
| OECD | Organisation for Economic Co-operation and Development |
| P | parental generation |
| PMRA | Pest Management Regulatory Agency |
| PND | postnatal day |
| PPE | personal protective equipment |
| ppm | parts per million |
| PRVD | Proposed Re-evaluation Decision |
| RBC | red blood cells |
| rel | relative |
| RNA | ribonucleic acid |
| SOP | standard operating procedure |
| TGF-β | transforming growth factor beta |
| Th | T-helper |
| TSLP | thymic stromal lymphopoietin |
| TSMP | Toxic Substances Management Policy |
| USEPA | United States Environmental Protection Agency |
| wt | weight/weights |

# Appendix I Tables and figures

**Table 1 Toxicology reference values for use in health risk assessment for DDAC**

| Exposure scenario | Study | Point of departure and endpoint | Target MOE[1] |
|---|---|---|---|
| Long-term dermal (adults, youth)[3] | Rat and rabbit oral developmental toxicity studies (co-critical) | Adjusted developmental NOAEL = 0.05 mg/kg bw/day (1 mg/kg bw/day corrected for 5% oral absorption)[2]<br><br>Delayed ossification and variations observed in the presence of maternal toxicity | 100 |
| Long-term dermal (children) | Rat 90-day dermal toxicity study | NOAEL = 12 mg/kg bw/day (highest dose tested)<br><br>Absence of systemic toxicity in the presence of severe dermal irritation | 100 |
| Long-term inhalation (adults) | Rat 28-day inhalation toxicity study | LOAEC = 0.091 mg/m$^3$ (0.02 mg/kg bw/day)<br><br>Respiratory tract inflammation and decreased body weight | 1000 |
| Long-term incidental oral (children 1–2 years old) | Rat and rabbit oral developmental toxicity studies (co-critical) | Maternal NOAEL = 1 mg/kg bw/day<br><br>Clinical signs of toxicity (audible respiration, hypoactivity) | 100 |
| Long-term aggregate (children 1–2 years old)<br><br>Oral and dermal | No endpoint common to the oral and dermal routes was identified for children 1–2 years old; therefore, an aggregate assessment for this sub-population is not required. | | |
| Long-term aggregate (adults)<br><br>Dermal[3] and inhalation[4] | Dermal and inhalation:<br><br>Rat and rabbit oral developmental toxicity studies (co-critical) | Common endpoint: Delayed ossification and variations observed in the presence of maternal toxicity<br><br>Dermal and inhalation: Adjusted developmental NOAEL = 0.05 mg/kg bw/day (1 mg/kg bw/day corrected for 5% oral absorption)[2] | Dermal and inhalation: 100 |
| Dermal sensitization | LLNA in mice | $EC_3$ = 0.17% (42.5 µg/cm$^2$)<br>Induction of dermal sensitization | 100 |
| Cancer | No treatment-related tumours were observed, therefore a cancer risk assessment is not required. | | |

[1] MOE (margin of exposure) refers to a target MOE for occupational and residential assessments.

[2] The oral NOAEL of 1 mg/kg bw/day, which represents an externally administered dose level, was adjusted to 0.05 mg/kg bw/day to correct for an approximate oral absorption estimation of 5% to allow for extrapolation to systemic exposure estimates via the dermal or inhalation route of exposure. [3] Since an oral NOAEL was selected, a dermal absorption factor of 100% was used in a route-to-route extrapolation.
[4] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (standard value) was used in route-to-route extrapolation.

**Table 2 Toxicity profile of technical DDAC**

Effects observed in both sexes are presented first, followed by sex-specific effects in males, then females, each separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| Absorption, distribution, metabolism and excretion – single and repeated oral low dose and single oral high dose (gavage)<br><br>Sprague-Dawley rat<br><br>PMRA No. 1236494, 1236495 | Rats received a single oral low dose (5 mg/kg bw) or a single high oral dose (50 mg/kg bw) of $^{14}$C-DDAC in distilled water. Additional groups of rats were administered diet containing 34 ppm of unlabelled DDAC for 14 days followed by a gavage dose of $^{14}$C-DDAC at 5 mg/kg bw on day 15.<br><br>**Rate and extent of absorption and excretion:** Absorption was limited. Radioactivity was primarily excreted in the feces in both sexes (89–99% of the AD). Urine accounted for 1.2–2.4% of the AD. The majority of the radioactivity was excreted within 72 hours. Note that biliary excretion was not assessed in this study, but was reported in a review of the hazard information for DDAC published in the scientific literature (PMRA No. 3550218). In the review article, in which it was also reported that DDAC was found to be poorly absorbed in rats via the oral route, with total oral absorption estimated to be between 3% and 7% based on urinary (0.9–3.2%) and biliary (1.8–4.0%) excretion.<br><br>**Distribution/target organ(s):** Tissue residues were very low after all dosing regimens (0.003–0.675%), indicating very little deposit of the test article. Highest residue levels as % of the AD were detected in liver, GIT, and kidneys. Highest residue levels as ppm were measured in adrenal gland, thyroid gland, heart, pancreas, liver and kidney.<br><br>**Toxicologically significant compound(s):** Analysis of feces indicated mostly unchanged DDAC (54–66%/37–59% of fecal |

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| | radioactivity in ♂/♀). Four minor metabolites were noted, formed from oxidative modification of the decyl side chain. Females demonstrated a more extensive metabolism of DDAC than males. No assessment of urinary metabolites was conducted due to low levels of radioactivity detected in urine. |
| Acute oral<br><br>Wistar rat<br><br>PMRA No. 1238158 | $LD_{50}$ = 450 mg/kg bw (♂/♀)<br><br>Clinical signs of toxicity included diarrhea, dehydrated appearance, and depression.<br><br>**High acute toxicity** |
| Acute oral<br><br>Sprague-Dawley rat<br><br>PMRA No. 1145748 | $LD_{50}$ = 238 mg/kg bw (♂/♀)<br><br>Clinical signs of toxicity included urine and fecal stains, salivation, dried red stains, eye squinting, piloerection, ataxia, body tremors, laboured and shallow respiration, depression, red discharge from mouth, bloated abdomen, abdominal spasms.<br><br>**High acute toxicity** |
| Acute dermal<br><br>New Zealand White rabbit<br><br>PMRA No. 1238159 | $LD_{50}$ = 4350 mg/kg bw (♂/♀)<br><br>Clinical signs of toxicity included depression. Severe dermal irritation noted at application sites.<br><br>**Low acute toxicity** |
| Acute inhalation | Testing was waived based on the corrosive nature of DDAC.<br><br>**High acute toxicity** |
| Eye irritation<br><br>New Zealand White rabbit<br><br>PMRA No. 1135426 | Extreme corneal opacity, iritis, and conjunctival irritation within 1 hour of instillation into the eye of one animal. The study was terminated after 1 hour for humane reasons.<br><br>**Corrosive to eyes** |
| Dermal irritation<br><br>New Zealand White rabbit<br><br>PMRA No. 1135428 | Severe dermal irritation persisted to 24 hours following application in the single animal tested. Observation included coriaceous texture, blanching, and necrosis. The study was terminated after 24 hours for humane reasons.<br><br>**Corrosive to skin** |
| Dermal sensitization (Buehler)<br><br>Hartley guinea pig | Negative |

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| PMRA No. 1011676 | |
| 90-day oral (diet)<br><br>CD-1 mouse<br><br>PMRA No. 1226313 | NOAEL = 107/134 mg/kg bw/day (♂/♀)<br>LOAEL = 182/224 mg/kg bw/day (♂/♀)<br><br>Effects at the LOAEL included: ↓ bwg (♂/♀); mononuclear cell infiltrate in liver (♂); ↑ rel. brain wt, thymic hemorrhage (♀). |
| 90-day oral (diet)<br><br>Sprague-Dawley rat<br><br>PMRA No. 1226312 | NOAEL = 61/74 mg/kg bw/day (♂/♀)<br>LOAEL estimated to be greater than 150 mg/kg bw/day (♂/♀)<br><br>Effects at LOAEL included: mortality, emaciation, unkempt appearance, pallor, hunched posture, loose feces, urinary staining, perianal redness, ↓ fc, bw loss, ↓ bwg, ↓ glucose, ↓ total protein, ↓ abs. liver wt., ↓ abs. kidney wt, ↑ rel. brain wt (♂/♀); ↑ RBC, ↑ HGB, ↑ HCT, ↑ phosphorus, ↑ rel. adrenal wt, ↑ rel. testes wt (♂); ↓ albumin, ↓ globulin, ↓ chloride (♀).<br><br>Test material intake at the LOAEL could not be accurately determined due to confounding mortality and food spillage. |
| 1-year oral (gavage)<br><br>Beagle dog<br><br>PMRA No. 1239055 | NOAEL = 3 mg/kg bw/day (♂/♀)<br>LOAEL = 10 mg/kg bw/day (♂/♀)<br><br>Effects at the LOAEL included soft feces (♂/♀); ↑ emesis, ↓ bw (♂). |
| 90-day dermal<br><br>Sprague-Dawley rat<br><br>PMRA No. 1226314 | Systemic NOAEL = 12 mg/kg bw/day (♂/♀)<br>Systemic LOAEL not determined as no treatment-related systemic effects were noted.<br><br>Dermal irritation was noted at all dose levels (2 mg/kg bw/day and higher). |
| 28-day inhalation (nose only)<br><br>Sprague-Dawley<br><br>Findings based on review by USEPA (PMRA No. 3510611; 3558884) | NOAEC not determined<br>LOAEC = 0.091 mg/m$^3$ (equivalent to 0.02/0.03 mg/kg bw/day in ♂/♀)<br><br>Effects at the LOAEC included: ↑ mucus in respiratory epithelium, ↑ total bronchoalveolar protein (♂/♀); ↓ bw, ↓ bwg, ↓ fc, ↓ serum glucose, ↑ rel. lung wt, ↑ total bronchoalveolar epithelial cell count (♂); ↑ bronchoalveolar LDH (♀).<br><br>Effects at higher concentrations included: degeneration of nasal cavity olfactory epithelium, subacute inflammation of the larynx, ulceration of stratified squamous epithelium of the nasal cavity, mild squamous metaplasia of the nasal cavity olfactory epithelium (♂ only), and subacute lung inflammation (♀ only). |

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| | Some effects at the highest concentration tested persisted after a 14-day recovery period, including ulceration of stratified squamous epithelium of nasal cavity (1/sex), minimal increased mucus in respiratory epithelium (1♀), and subacute inflammation of larynx (1♀). |
| 18-month oncogenicity (diet)<br><br>CD-1 mouse<br><br>PMRA No. 1236493 | NOAEL = 76/93 mg/kg bw/day (♂/♀)<br>LOAEL = 156/193 mg/kg bw/day (♂/♀)<br><br>Effects at the LOAEL included: ↓ bw, ↓ overall bwg, ↓ liver wt (♂/♀)<br><br>No evidence of tumourigenicity |
| 2-year chronic toxicity / oncogenicity (dietary)<br><br>Sprague-Dawley rat<br><br>PMRA No. 1239056, 1239057 | NOAEL = 32/41 mg/kg bw/day (♂/♀)<br>LOAEL = 64/83 mg/kg bw/day (♂/♀)<br><br>Effects at the LOAEL included: ↓ bw, ↓ bwg, ↓ fc, lesions of mesenteric lymph nodes (blood in sinuses, hemosiderosis, histiocytosis) (♂/♀); ↓ urine volume, ↑ urine specific gravity, ↓ lymphocytes, bile duct hyperplasia (♀)<br><br>No evidence of tumourigenicity |
| 2-generation reproductive toxicity (diet)<br><br>Sprague-Dawley rat<br><br>PMRA No. 1236492 | Parental NOAEL = 48/59 mg/kg bw/day (♂/♀)<br>Parental LOAEL = 101/120 mg/kg bw/day (♂/♀)<br><br>Parental effects at the LOAEL included: ↓ pre-mating bw (P), ↓ pre-mating bwg (P, $F_1$), ↓ pre-mating fc (P, $F_1$) (♂/♀); ↓ bw during gestation and lactation (P, $F_1$), ↑ bwg during lactation (P, $F_1$) (♀); histiocytosis and hemosiderosis of mediastinal lymph node ($F_1$) (♂).<br><br>Offspring NOAEL = 59 mg/kg bw/day (♂/♀)<br>Offspring LOAEL = 120 mg/kg bw/day (♂/♀)<br><br>Offspring effects at the LOAEL included: ↓ bw ($F_1$ and $F_2$; PND 21), ↓ bwg ($F_1$ and $F_2$).<br><br>Reproductive NOAEL = 101/120 mg/kg bw/day (♂/♀)<br>Reproductive LOAEL not determined as no treatment-related effects were observed on measured reproductive parameters (mating, gestation or fertility indices; live births; sex ratio; birth weight).<br><br>No evidence of sensitivity of the young |

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| Developmental toxicity (gavage)<br><br>Sprague-Dawley rat<br><br>PMRA No. 1239058 | Maternal NOAEL = 1 mg/kg bw/day<br>Maternal LOAEL = 10 mg/kg bw/day<br><br>Maternal effects at the LOAEL included: audible respiration (GD 6-21).<br><br>Maternal effects at the highest dose level (20 mg/kg bw/day) included: gasping, perinasal or perioral encrustation, urine stains, loose feces, unkempt appearance, ↓ bwg, gas-filled intestines, stomach ulcerations.<br><br>Developmental NOAEL = 1 mg/kg bw/day<br>Developmental LOAEL = 10 mg/kg bw/day<br><br>Developmental effects at the LOAEL included: ↑ delayed ossification (poorly ossified thoracic centrum #10 and #12; poorly ossified sternebra #4).<br><br>Developmental effects at highest dose level (20 mg/kg bw/day) included: ↑ skeletal variations and delayed ossification (split anterior arch of the atlas; poorly ossified thoracic centrum #1, 10 and 12; bilobed thoracic centrum #11; unilateral short rib #13; poorly ossified parietal; poorly ossified sternebra #4).<br><br>No treatment-related malformations<br>No evidence of sensitivity of the young |
| Developmental toxicity (gavage)<br><br>New Zealand White rabbit<br><br>PMRA No. 1226315 | Maternal NOAEL = 1 mg/kg bw/day<br>Maternal LOAEL = 3 mg/kg bw/day<br><br>Maternal effects at the LOAEL included: ↓ bwg during dosing period, audible respiration, hypoactivity, colour change of the stomach and liver.<br><br>Maternal effects at the highest dose level (10 mg/kg bw/day) included: mortality, bw loss, laboured respiration, gasping, abdominal breathing, ↓ gravid uterine wt.<br><br>Developmental NOAEL = 1 mg/kg bw/day<br>Developmental LOAEL = 3 mg/kg bw/day<br><br>Developmental effects at the LOAEL included: small gallbladder, poorly ossified parietal bone.<br><br>Developmental effects at the highest dose level (10 mg/kg bw/day) |

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| | included: ↑ number of dead fetuses/litter, ↓ fetal bw.<br><br>No treatment-related malformations<br>No evidence of sensitivity of the young |
| Bacterial reverse gene mutations in vitro<br><br>S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA1538<br><br>PMRA No. 1214219 | Negative ± metabolic activation<br><br>Tested up to cytotoxic concentrations. |
| Forward gene mutations in mammalian cells in vitro<br><br>Chinese hamster ovary cells (HGPRT locus)<br><br>PMRA No. 1226288 | Negative ± metabolic activation<br><br>Tested up to cytotoxic concentrations. |
| Unscheduled DNA synthesis in vitro<br><br>Rat primary hepatocytes<br><br>PMRA No. 1226301 | Negative ± metabolic activation<br><br>Tested up to cytotoxic concentrations. |
| Chromosome aberrations in vitro<br><br>Chinese hamster ovary cells<br><br>PMRA No. 1214218 | Negative ± metabolic activation<br><br>Tested up to cytotoxic concentrations. |
| In vivo cytogenetics (gavage)<br><br>Sprague-Dawley rat<br><br>PMRA No. 1214220 | Negative<br><br>Tested at the maximum tolerated dose.<br><br>Clinical signs of toxicity included piloerection, hunched posture, lethargy, decreased respiration, ptosis, pallor of extremities, diarrhea, walking on toes, ataxia, thinness, and bloated abdomen. |

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| **Studies of interest located in the published scientific literature** | |
| 14-day inhalation toxicity (whole body)<br><br>Sprague-Dawley rat<br><br>PMRA No. 3550087 | Supplemental (some limitations in reporting; raw data not available)<br><br>Effects at ≥ 0.6 mg/m$^3$ included: inflammatory cell infiltration and interstitial pneumonia, thickening of alveolar walls. |
| 90-day inhalation toxicity (whole body)<br><br>Sprague-Dawley rat<br><br>PMRA No. 3550088 | Supplemental (some limitations in reporting; raw data not available)<br><br>Effects at ≥ 0.36 mg/m$^3$ included: ↑ polymorphonuclear leukocytes, ↑ lymphocytes, ↓ macrophages, inflammatory cell infiltration and interstitial pneumonia (♂/♀); ↑ lung wt (♀). |
| Acute pulmonary toxicity and inflammation (intratracheal instillation)<br><br>Sprague-Dawley rat (♂ only)<br><br>PMRA No. 3550089 | Supplemental (some limitations in reporting; raw data not available)<br><br>Animals were sacrificed 1 or 7 days after intratracheal instillation of DDAC (the purity of DDAC was not reported) and ethylene glycol. Bronchoalveolar lavage fluid (BALF) was collected for analysis of lung cell damage and pulmonary inflammation.<br><br>It was reported in the study BALF protein content and inflammatory cell recruitment in the lung still remained elevated at 7 days after the administration of DDAC with the higher dose of ethylene glycol, suggesting that the combination of DDAC and ethylene glycol can synergistically induce pulmonary cytotoxicity and inflammation, and that ethylene glycol appears to amplify the harmful effects on DDAC on the lung. |
| Acute pulmonary toxicity and inflammation (intratracheal instillation)<br><br>C57BL/6J mouse (♂ only)<br><br>PMRA No. 3550090 | Supplemental (some limitations in reporting; raw data not available)<br><br>Animals were sacrificed 3, 7, 13, or 20 days after intratracheal instillation of a DDAC formulation in saline (reported to contain 87.2% DDAC). BALF was collected for analysis of lung cell damage and pulmonary inflammation.<br><br>It was reported in the study that pulmonary inflammation peaked on day 7, and that the inflammatory phase was accompanied or followed by pulmonary remodelling and fibrosis. |

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| Acute pulmonary toxicity and inflammation (intratracheal instillation)<br><br>C57BL/6J mouse (♂ only)<br><br>PMRA No. 3550091 | Supplemental (some limitations in reporting; raw data not available)<br><br>Animals were sacrificed 1, 3, or 7 days after intratracheal instillation of a DDAC formulation in saline (reported to contain 87.2% DDAC). BALF was collected for analysis of lung cell damage and pulmonary inflammation.<br><br>It was reported in the study that pulmonary cytotoxicity was evident on days 1 and 7, and that inflammation peaked on day 7. |
| Acute pulmonary toxicity and inflammation (intratracheal instillation)<br><br>C57BL/6J mouse (♂ only)<br><br>PMRA No. 3550092 | Supplemental (some limitations in reporting; raw data not available)<br><br>Animals were sacrificed 1, 3, or 7 days after intratracheal instillation of a DDAC formulation in saline (reported to contain 87.2% DDAC). Lungs were processed for histological examination and immunohistochemical analysis. Additionally, lung fibroblasts from untreated mice were incubated in the DDAC formulation for RNA and protein analyses to further evaluate TGF-β signaling.<br><br>It was reported in the study that fibrotic foci were observed in the lungs on day 3, and were widely extended on day 7, with evidence of increased α smooth muscle actin-positive mesenchymal cells and upregulation of Type I procollagen mRNA. In isolated lung fibroblasts, the mRNA levels of TGF-β were specifically increased by DDAC treatment, which were abolished by treatment with a TGF-β kinase inhibitor. |
| Evaluation of the irritancy and hypersensitivity potential following (dermal – modified LLNA)<br><br>BALB/c mouse (♀ only)<br><br>PMRA No. 3550096 | Positive for dermal sensitization<br><br>$EC_3$ = 0.17% (equivalent to 42.5 μg/cm$^2$)<br><br>It was reported in the study that DDAC induced significant irritancy (at concentrations of 0.5 and 1%), evaluated by ear swelling. A concentration-dependent increase in lymphocyte proliferation was observed with a calculated $EC_3$ value of 0.17%. Dermal exposure to DDAC did not induce increased production of IgE as evaluated by phenotypic analysis of draining lymph node B-cells (IgE+B220+) and measurement of total serum IgE levels. Additional phenotypic analyses revealed significant and dose-responsive increases in the absolute number of B-cells, CD4+ T-cells, CD8+ T-cells and dendritic cells in the draining lymph nodes, along with significant increases in the percentage of B-cells (at concentrations of 0.25% and 1% DDAC) at Day 10 following 4 |

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| | days of dermal exposure. There was also a significant and dose-responsive increase in the number of activated CD44 + CD4 + and CD8+ T-cells and CD86+ B-cells and dendritic cells following exposure to all concentrations of DDAC. These results demonstrate the potential for development of irritation and hypersensitivity responses to DDAC following dermal exposure.<br><br>These findings demonstrate a lack of increase in both local and total IgE, along with an increased percentage of activated CD8+ T-cells in the draining lymph nodes following exposure; this data suggests that DDAC may induce a T-cell or TH1-mediated hypersensitivity response. |
| Potential classification of chemical immunologic response based on gene expression profiles (dermal – modified LLNA)<br><br>BALB/c mouse<br><br>PMRA No. 3550100 | Supplemental (some limitations in reporting; raw data not available)<br><br>It was reported in the study that DDAC caused an increase in the mRNA expression of the danger signals TSLP (skin), and S100a8 (skin, blood, lung). Additionally, DDAC decreased expression of the cellular adhesion molecule E-cadherin. |
| Assessment of immunological mechanism following topical exposure (dermal – modified LLNA)<br><br>BALB/c mouse<br><br>PMRA No. 3550101 | Supplemental (some limitations in reporting; purity of DDAC unknown; raw data not available)<br><br>It was reported in the study that DDAC exposure resulted in a rapid and dramatic increase in the Th2-skewing and ILC2 activating cytokine thymic stromal lymphopoietin. Correspondingly, dermal ILC2s were activated 24 hours after DDAC exposure, resulting in increased expression of CD25, ICOS and KLRG1, and decreased CD127 throughout 7 days of exposure. Following ILC2 activation, the Th2 cytokine IL-4 was elevated compared to control mice in total ear protein lysate (0.5% DDAC). Rag2−/− mice were used to determine a functional role for ILC2s in DDAC induced sensitization. ILC2s from Rag2−/− mice were similarly activated by DDAC and, importantly, produced significant levels of IL-4 and IL-5 in the skin (0.5% DDAC). The study authors concluded that these data indicate that ILC2s contribute to early Th2 immune responses following DDAC exposure. ILC2s have been previously implicated in allergic responses, but to their knowledge have not been thoroughly investigated in chemical sensitization. These results indicate that following DDAC exposure, skin ILC2s become activated and produce Th2 cytokines, providing a possible |

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| | mechanism for the development of the mixed-type allergic response. |
| Immune response following co-exposure with other compounds (dermal – modified LLNA)<br><br>BALB/c mouse<br><br>PMRA No. 3550102 | Supplemental (some limitations in reporting; purity of DDAC unknown; raw data not available)<br><br>It was reported in the study that co-exposure of DDAC with ortho-phthalaldehyde resulted in phenotypic changes in draining lymph node cells, including a decreased frequency of CD8+ T cells and increased frequency and number of B cells compared with DDAC-only treated mice. The co-exposed mice also had enhanced Th2 responses, including significant alterations in: Il4 (increased), B-cell activation (increased), CD8+ T-cell activation (decreased), and local and systemic IgE production (increased). These changes were not<br>observed if mice were exposed to DDAC prior to ortho-phthalaldehyde. The study authors suggested that these results may partially explain the discordance between epidemiological and laboratory studies regarding disinfectants and provide insight into the potential immunological implications of mixed chemical exposures. |
| Prediction of the skin sensitization potential (in vitro)<br><br>human Cell Line Activation Test (h-CLAT) and Direct Peptide Reactivity Assay (DPRA)<br><br>PMRA No. 3550103 | Supplemental (some limitations in reporting; purity of DDAC unknown; raw data not available)<br><br>It was reported in the study that mixtures of DDAC with ethylene glycol at ratio of 7:3 and 1:4 w/v were all positive by the h-CLAT in terms of skin sensitization potential but skin sensitization potency was mitigated as the proportion of ethylene glycol increased. DDAC and its ethylene glycol mixtures were all negative by the DPRA. |
| Patch testing with human volunteers<br><br>PMRA No. 3550104 | Supplemental (some limitations in reporting; purity of DDAC unknown; raw data not available)<br><br>It was reported that patch testing in 84 volunteers with DDAC at 0.05% resulted in five patients with weakly positive reactions, without clinical relevance. Patch testing with DDAC at 0.03% showed no positive reactions on day 3 readings. |
| Patch testing with human volunteers<br><br>PMRA No. 3550105 | Supplemental (some limitations in reporting; raw data not available)<br><br>It was reported that, of 12 volunteers, none reacted to 0.01% DDAC, but 7 weak positive reactions and 2 erythematous (doubtful) reactions to 0.1% DDAC were observed at day 3. |

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| | Clinical relevance could be confirmed in 2 DDAC-positive volunteers with occupational hand dermatitis, both of which were exposed to DDAC-containing surface disinfectants. In the other 5 patients with positive reactions to DDAC, the available information did not reveal current exposure to DDAC. |
| Quaternary ammonium compounds in hypersensitivity reactions<br><br>Review article<br><br>PMRA No. 3550225 | Supplemental (review article)<br><br>It was reported that there is growing evidence concerning the implication of quaternary ammonium compounds in hypersensitivities. Distinguishing the irritant or sensitizing properties of chemicals is complex and as a result, the sensitizing property of quaternary ammonium compounds is still controverted. Moreover, the precise mechanisms underlying the possible sensitization effect are still under investigation, and to date, only a few studies have documented an immunological mechanism. Besides, quaternary ammonium compounds have been suggested to be responsible for neuromuscular blocking agents sensitization by cross-reactivity. This hypothesis is supported by a higher prevalence of quaternary ammonium-specific IgE in the professionally exposed populations, such as hairdressers, cleaners, or healthcare workers, suggesting that the sensitization happens with structurally similar compounds present in the environment. |
| Quaternary ammonium compounds and contact dermatitis: A review and considerations during the COVID-19 pandemic<br><br>Review article<br><br>PMRA No. 3550110 | Supplemental (review article)<br><br>It was reported in the study that several case reports have highlighted DDAC-containing products as a source of contact dermatitis. Quaternary ammonium compounds may cause irritancy and contact dermatitis, and should be used cautiously in patients with compromised skin barriers. Reported reactions include ulcerative skin lesions, hyperpigmentation, and erythema. Given their widespread utilization, additional research is needed to better classify their dermal effects and identify other cross-reactors. |
| Assessment of neural tube defects following ambient and direct exposure to quaternary ammonium disinfectants (ambient exposure, diet, gavage)<br><br>Sprague-Dawley rat (ambient exposure only) | Supplemental (Some limitations in reporting; test material was a formulated product; raw data not available; ambient exposure to quaternary ammonium compounds was not entirely controlled.)<br><br>It was reported that introduction of a formulated cleaner containing 6.76% ADBAC and 10.1% DDAC in the vivarium caused neural tube defects (NTDs) in mice and rats. The NTDs persisted for two generations after cessation of exposure. Notably, male exposure alone was sufficient to cause NTDs. Equally significant, ambient exposure from disinfectant use in the vivarium, influenced the levels of NTDs to a greater extent than |

| Study type/ Animal/PMRA No. | Study results |
|---|---|
| CD-1 mouse (ambient exposure, diet, and gavage)<br><br>PMRA No. 3550093 | oral dosing. No gross or significant axial skeletal malformations were observed in late gestation fetuses. NTDs, placental abnormalities and late gestation fetal deaths were increased in mice following 8 weeks of exposure to the formulated cleaner via the diet at 120 mg/kg bw/day prior to mating. Increased NTDs were also observed when ♂ mice were gavage dosed every other day for 10 days with 30 mg/kg bw/day prior to mating, and ♀ mice were dosed once on GD 8 with 15 mg/kg bw/day. However, NTDs were also evident in some control animals, suggesting continued environmental exposure. |
| Assessment of fertility (diet)<br><br>CD-1 mouse<br><br>PMRA No. 3550094 | Supplemental (some limitations in reporting including unclear reporting of protocol; test material was a formulated product; raw data not available)<br><br>It was reported that breeding pairs exposed to a commercial disinfectant containing 6.7% ADBAC and 10.1% DDAC for six months at 120 mg/kg bw/day exhibited decreases in fertility and fecundity, increased time to first litter, longer pregnancy intervals, fewer pups per litter and fewer pregnancies. Significant morbidity in near term dams was also observed. |
| Assessment of fertility (diet)<br><br>CD-1 mouse<br><br>PMRA No. 3550095 | Supplemental (some limitations in reporting; test material was a formulated product; only one dose level used; raw data not available)<br><br>It was reported that the numbers of corpora lutea and viable embryos were decreased after 8 weeks of exposure to a commercial disinfectant containing 6.7% ADBAC and 10.1% DDAC at 120 mg/kg bw/day in drinking water. Dams exposed for 2 weeks to 120 mg/kg bw/day of the commercial disinfectant in the diet spent significantly less time in estrus. Sperm analyses of ♂ mice gavage dosed with the commercial disinfectant for 8 days at 7.5 mg/kg bw/day revealed reduced sperm count. |

**Table 3 Use (label) claims proposed by the applicant and whether supported or unsupported**

| Supported uses | Supported use rate |
|---|---|
| Polymer dispersions, latices, solutions, and resins. | Add 0.02–0.2 kg to 100 kg of product to provide 100–1000 ppm didecyl dimethyl ammonium chloride. |

# References

## A. List of Studies/Information Submitted by Registrant

### 1.0 Human and Animal Health

| PMRA Document Number | Reference |
|---|---|
| 3299700 | 2020, Acticide DDQ 50-E Use Description Scenario, DACO: 5.2 |
| 3510610 | 2023, DDAC Waiver for 28 Day Inhalation Study, DACO: 4.3.7 |
| 3510611 | 2016, Subchronic inhalation toxicity study of DDAC - EPA DER, DACO: 4.3.7 |
| 1236494 | 1989, Addendum to Report Entitled "Absorption, Distribution, Metabolism and Excretion Studies of Didecyldimethylammoniumchloride (DDAC) in the Rat (P01421), DACO: 4.5.9 |
| 1236495 | 1989, Absorption, Distribution, Metabolism and Excretion Studies of Didecyldimethylammoniumchloride (DDAC) in the Rat, DACO: 4.5.9 |
| 1238158 | Bardac 2250/80 - Acute Oral LD50 in Rats, DACO: 4.2.1 |
| 1145748 | Acute Oral Toxicity in Rats-Median Lethal Dosage Determination with Didecyldimethylammoniumchloride (DDAC)(91-8114-21(A)) (Bardac 2280), DACO: 4.2.1 |
| 1238159 | Bardac 2250/80 - Acute Dermal LD50 in Rabbits, DACO: 4.2.2 |
| 1135426 | Primary Eye Irritation Study in Rabbits with Didecyldimethylammoniumchloride (DDAC) (91-8114-21(C))(Bardac 2280), DACO: 4.2.4 |
| 1135428 | Primary Skin Irritation Study in Rabbits with Didecyldimethylammoniumchloride (DDAC) (91-8114-21(B))(Bardac 2280), DACO: 4.2.5 |
| 1011676 | 2004, Bardac 2280 Dermal Sensitization Test in Guinea Pigs, DACO: 4.2.6 |
| 1226313 | 1988, Subchronic Dietary Dose Range Finding Study with DDAC in Mice (51-507), DACO: 4.3.1,4.3.8 |
| 1214214 | 1975, 90-Day Feeding Study in Dogs, DACO: 4.3.1 |
| 1226314 | Ninety-Day Subchronic Dermal Toxicity Study with DDAC in Rats (51-554), DACO: 4.3.4 |
| 1236493 | 1991, Chronic Dietary Oncogenicity Study with Didecyldimethylammoniumchloride in Mice, DACO: 4.4.1,4.4.2 |

| | |
|---|---|
| 1239056 | 1991, Chronic Dietary Toxicity/Oncogenicity Study with Didecyldimethylammoniumchloride in Rats, DACO: 4.4.1,4.4.2 |
| 1239057 | Chronic Dietary Toxicity/Oncogenicity Study with Didecyldimethylammoniumchloride in Rats, DACO: 4.4.1,4.4.2 |
| 1214218 | 1986, Chromosomal Aberrations Assay with Chinese Hamster Ovary Cells In Vitro (4236), DACO: 4.5.4 |
| 1214219 | 1982, Salmonella/Mammalian - Microsome Assay with Bardac 22, DACO: 4.5.4 |
| 1214220 | 1987, Analysis of Metaphase Chromosomes Obtained from Bone Marrow of Rats... (LZA 24/8761), DACO: 4.5.4 |
| 1226288 | 1988, Mutagenicity Test on DDAC in the CHO/HGPRT Forward Mutation Assay (10141-0-435), DACO: 4.5.4 |
| 1226301 | 1998, Mutagenicity Test on DDAC In The Rat Primary Hepatocute Unscheduled DNA Synthesis Assay (10141-0-447), DACO: 4.5.4 |
| xzc1226312 | 1988, Ninety-Day Dietary Subchronic Oral Toxicity Study with DDAC in Rats (51-506), DACO: 4.3.1 |
| 1226315 | 1989, Developmental Toxicity Study of DDAC Administered by Gavage to New Zealand White Rabbits (51-590), DACO: 4.5.2 |
| 1236492 | 1991, Two-Generation Reproduction Study in Sprague-Dawley (CD) Rats with Didecyldimethylammoniumchloride Administered in the Diet (52-648), DACO: 4.5.1 |
| 1239055 | 1991, Chronic Oral Toxicity Study of Didecyldimethylammonuimchloride in Dogs. Final Report, DACO: 4.3.1 |
| 1239058 | 1991, Developmental Toxicity Evaluation of Didecyldimethylammoniumchloride Administered by Gavage to CD (Sprague-Dawley) Rats, DACO: 4.5.2 |


## 2.0 Value


| PMRA Document Number | Reference |
|---|---|
| 3299699 | 2019, To Provide Efficacy Data for Acticide 50-E in Polymers, DACO 10.2 |

## i) Published Information

### 1.0 Human and Animal Health


| PMRA Document Number | Reference |
|---|---|
| 3550087 | Cheol-Hong Lim and Yong-Hyun Chung, 2014, Effects of Didecyldimethylammonium Chloride on Sprague-Dawley Rats after Two Weeks of Inhalation Exposure, Toxicol. Res., Vol. 30, No. 3, pp. 205-210 (2014), DACO: 12.5.4 |
| 3550088 | Yong-Soon Kim, Sung-Bae Lee and Cheol-Hong Lim, 2017, Effects of Didecyldimethylammonium Chloride (DDAC) on Sprague-Dawley Rats after 13 Weeks of Inhalation Exposure, Toxicol. Res., Vol. 33, No. 1, pp. 7-14 (2017), DACO: 12.5.4 |
| 3550089 | Do Young Kwon, Hyun-Mi Kim, Eunji Kim, Yeon-Mi Lim, Pilje Kim, Kyunghee Choi and Jung-Taek Kwon, 2016, Acute pulmonary toxicity and inflammation induced by combined exposure to didecyldimethylammonium chloride and ethylene glycol in rats, J. Toxicol. Sci., Vol. 41, No. 1, pp. 17-24 (2016), DACO: 12.5.4 |
| 3550090 | Aya Ohnuma, Toshinori Yoshida, Haruka Tajima, et al, 2010, Didecyldimethylammonium chloride induces pulmonary inflammation and fibrosis in mice, , Experimental and Toxicologic Pathology, Vol. 62, pp. 643-651 (2010), DACO: 12.5.4 |
| 3550091 | Aya Ohnuma, Toshinori Yoshida, Haruka Horiuchi, et al., 2011, Altered pulmonary defense system in lung injury induced by didecyldimethylammonium chloride in mice, Inhalation Toxicology, Vol. 23, No. 8, pp. 476-485 (2011), DACO: 12.5.4 |
| 3550092 | Aya Ohnuma-Koyoma, Toshinori Yoshida, Haruka Tajima-Horiuchi, et al, 2013, Didecyldimethylammonium chloride induces pulmonary fibrosis in association with TGF-B signaling in mice, Experimental and Toxicologic Pathology, Vol. 65, pp. 1003-1009 (2013), DACO: 12.5.4 |
| 3550096 | Stacey E. Anderson, Hillary Shane, Carrie Long, et al, 2016, Evaluation of the irritancy and hypersensitivity potential following topical application of didecyldimethylammonium chloride, J. Immunotoxicol., Vol. 13, No. 4, pp. 557-566 (2016), DACO: 12.5.4 |
| 3550100 | Stacey E. Anderson, Rachel Baur, Michael Kashon, et al, 2020, Potential classification of chemical immunologic response based on gene expression profiles, J. Immunotoxicol., Vol. 17, No. 2, pp. 122-134 (2020), DACO: 12.5.4 |
| 3550101 | Hillary L. Shane, Ewa Lukomska, and Stacey E. Anderson, 2019, Topical application of the quaternary ammonium compound didecyldimethylammonium chloride activates type 2 innate lymphoid cells and initiates a mixed-type allergic response, Toxicol. Sci., Vol. 168, No. 2, pp. 508-518 (2019), DACO: 12.5.4 |

3550102 Hillary L. Shane, Ewa Lukomska, Lisa Weatherly, Rachel Baur, and Stacey E. Anderson, 2020, Prior exposure to ortho-phthaldehyde augments IgE-mediated immune responses to didecyldimethylammonium chloride: Potential for 2 commonly used antimicrobials to synergistically enhanced allergic disease, Toxicological Sciences, Vol. 178, No. 1, pp. 127-137 (2020), DACO: 12.5.4

3550103 JaeHee Lee, AhRang Cho, Ravi Gautam, et al, 2019, Prediction of skin sensitization potential of didecyldimethylammonium chloride and 3,7-dimethyl-2,6-octadienal and mixtures of these compounds with the excipient ethylene glycol through the human Cell Line Activation Test and the Direct Peptide Reactivity Assay, Toxicology and Industrial Health, Vol. 35, No. 8, pp. 507-519 (2019), DACO: 12.5.4

3550104 Katharina Kreipe, Susann Forkel, Kim-Elisabeth Heinemann, et al, 2021, Contact sensitizations to disinfectants containing alcohols or quarternary ammonium compounds are rarely of clinical relevance, Contact Dermatitis, Vol. 85, pp. 211-214 (2021), DACO: 12.5.4

3550105 Johannes Geier, Holger Lessmann, Naciye Cevik, et al., 2016, Patch testing with didecyldimethylammonium chloride, Contact Dermatitis, Vol. 74, pp. 373-384 (2016), DACO: 12.5.4

3550110 Chibudem AV Okeke, Ramona Khanna, Alison Ehrlich, 2023, Quaternary ammonium compounds and contact dermatitis: A review and considerations during the COVID-19 pandemic, Clinical, Cosmetic and Investigational Dermatology, Vol. 16, pp. 1721-1728 (2023), DACO: 12.5.4

3550218 Anthony Luz, Paul DeLeo, Nathan Pechacek, Mike Fremantle, 2020, Human health hazard assessment of quaternary ammonium compounds: Didecyl dimethyl ammonium chloride and alkyl (C12-C16) dimethyl benzyl ammonium chloride, Regulatory Toxicology and Pharmacology., Vol. 116, 104717 (2020)., DACO: 12.5.4

3550093 Terry C. Hrubec, Vanessa E. Melin, Caroline S. Shea, et al, 2017, Ambient and dosed exposure to quaternary ammonium disinfectants causes neural tube defects in rodents, Birth Defects Research, Vol. 109, No. 14, pp. 1166-1178 (2017), DACO: 12.5.4

3550094 Vanessa E. Melin, Haritha Potineni, Patricia Hunt, et al, 2014, Exposure to common quaternary ammonium disinfectants decreases fertility in mice, Reproductive Toxicology, Vol. 50, pp. 163-170 (2014), DACO: 12.5.4

3550095 Vanessa E. Melin, Travis E. Melin, Brian J. Dessify, et al, 2016, Quaternary ammonium disinfectants cause subfertility in mice by targeting both male and female reproductive processes, Reproductive Toxicology, Vol. 59, pp. 159-166 (2016), DACO: 12.5.4

3550225 Marine Peyneau, Luc de Chaisemartin, Nicolas Gigant, et al, 2022, Quaternary ammonium compounds in hypersensitivity reactions, Frontiers in Toxicology, Vol. 4, Article 973680 (2022), DACO: 12.5.4

3558884 USEPA, 2017. Didecyl Dimethyl Ammonium Chloride (DDAC) Final Work Plan, Registration Review Initial Docket Case Number 3003. March 2017