Proposed Re-evaluation Decision PRVD2022-10

1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin and hydroxymethyl-5,5-dimethylhydantoin and Associated End-use Products

Consultation Document

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Proposed re-evaluation decision for 1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin (DMY) and hydroxymethyl-5,5-dimethylhydantoin (MMY) and associated end-use products

Under the authority of the *Pest Control Products Act*, all registered pesticides must be re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports and other regulatory agencies. Health Canada applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin (DMY) and hydroxymethyl-5,5-dimethylhydantoin (MMY) are antimicrobial material preservatives used in a wide variety of products such as liquid detergents, soft soaps, room deodorizers and air fresheners, water-based surfactants, polymer emulsions, protective and decorative coatings, water-based gels for household and industrial products, textiles, water-based adhesives, latex for paper and coatings, and water-based inks. Currently registered products containing DMY and MMY can be found in the Pesticide Product Information Database and in Appendix I; all currently registered products contain both DMY and MMY. Appendix II lists all uses for which DMY/MMY is presently registered.

This document presents the proposed re-evaluation decision for DMY and MMY, including the proposed amendments (risk mitigation measures) to protect human health and the environment, as well as the science evaluation on which the proposed decision is based. All products containing DMY and MMY that are registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period,[1] during which the public (including the pesticide manufacturers and stakeholders) may submit written comments and additional information to PMRA Publications. The final re-evaluation decision will be published after taking into consideration the comments and information received during the consultation period.

Proposed re-evaluation decision for DMY and MMY

Under the authority of the *Pest Control Products Act* and based on an evaluation of available scientific information, Health Canada is proposing continued registration of DMY and MMY, and associated end-use products registered for sale and use in Canada.

DMY and MMY are of value in aiding in the prevention and control of bacterial and fungal contamination of aqueous-based materials. Such contaminations can lead to product failures of function or discolorations/unpleasant odours that will make the product unusable.

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

Risks to human health and the environment were shown to be acceptable when DMY and MMY are used according to the proposed conditions of registration, which include the mitigation measures identified below.

Risk mitigation measures

Human health

As a result of the re-evaluation of 1,3-bis (hydroxymethyl)-5,5-dimethylhydantoin (DMY) and hydroxymethyl-5,5-dimethylhydantoin (MMY), the PMRA is proposing further risk-reduction measures in addition to those already identified on DMY/MMY product labels. Additional revisions to the DMY/MMY labels are proposed, in order to meet the current labelling standards and for consistency.

To protect workers using end-use products during the manufacturing process:

- A closed transfer system for commercial-class liquid (solution) products.

To protect workers, updated label statements are required to reflect current standards for personal protective equipment (PPE).

To protect consumers, label statements are required to reflect current standards for paper and paperboard use.

Environment

To protect the environment, the following risk mitigation measure is proposed:

- An update to the label statement prohibiting effluent discharge

International context

Hydroxymethyl dimethylhydantoins (DMY and MMY) are currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the United States, the European Union, and Australia. In the United States, the use pattern for hydroxymethyl hydantoins is more extensive than the Canadian use pattern and includes metalworking fluids, starch solutions, paper and paperboard products. No decision by an OECD member country to prohibit all uses of hydroxymethyl dimethylhydantoins for health or environmental reasons has been identified.

Next steps

Upon publication of this proposed re-evaluation decision the public, including the registrants and stakeholders, are encouraged to submit additional information that could be used to refine risk assessments during the 90-day public consultation period.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of the re-evaluation decision document,[2] which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with Health Canada's responses.

Refer to Appendix I for details on specific products impacted by this proposed decision.

Other information

The relevant confidential test data on which the proposed decision is based (see the References section of this document) are available for public inspection, upon application, in Health Canada's Reading Room. For more information, please contact Health Canada's Pest Management Information Service.

Additional scientific information

No additional scientific data are required at this time.

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

Science evaluation

1.0 Introduction

DMY and MMY are registered for the preservation of various aqueous-based materials including liquid detergents, soft soaps, room deodorizers and air fresheners, water-based surfactants, polymer emulsions, protective and decorative coatings, water-based gels for household and industrial products, textiles, adhesives, latex for paper coatings, and water-based inks. DMY and MMY are hydantoins that function by releasing formaldehyde into solution to control bacterial and fungal growth and thus prevent microbial spoilage. Formaldehyde is very reactive and interacts with protein, combining with the primary amide and amino groups. It is also an alkylating agent reacting with the carboxyl, sulfhydryl and hydroxyl groups of DNA and RNA.

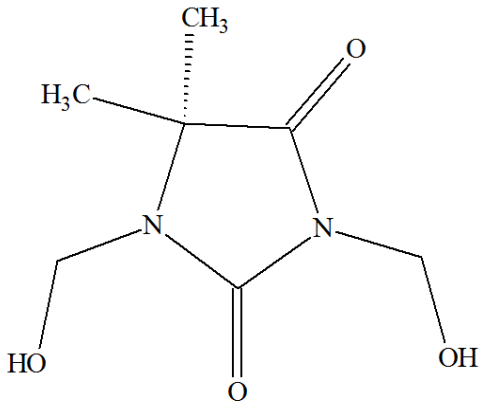
The active ingredients DMY and MMY are always found in combination within end-use products, and have been registered in Canada as material preservatives since 1998. Appendix I lists all DMY/MMY products that are registered under the authority of the *Pest Control Products Act*. Appendix II lists all uses for which DMY/MMY is presently registered.

2.0 Technical grade active ingredient

2.1 Identity

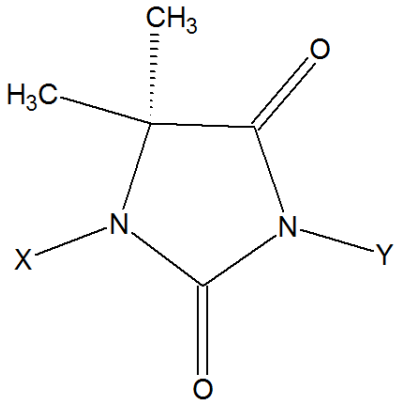
Common name	DMY: 1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin MMY: hydroxymethyl-5,5-dimethylhydantoin
Function	Material Preservative
Chemical family	Hydantoins
Chemical name	
1 International Union of Pure and Applied Chemistry (IUPAC)	DMY: 1,3-bis(hydroxymethyl)-5,5-dimethylimidazolidine-2,4-dione MMY: (hydroxymethyl)-5,5-dimethylimidazolidine-2,4-dione
2 Chemical Abstracts Service (CAS)	DMY: 2,4-imidazolidinedione, 1,3-bis(hydroxymethyl)-5,5-dimethyl- MMY: 2,4-imidazolidinedione, (hydroxymethyl)-5,5-dimethyl-
CAS Registry Number	DMY: 6440-58-0 MMY: 27636-82-4
Molecular formula	DMY: $C_7H_{12}N_2O_4$ MMY: $C_6H_{10}N_2O_3$

Structural formula



1,3-Bis(hydroxymethyl)-5,5-dimethylhydantoin

DMDMH
DMY



Hydroxymethyl-5,5-dimethylhydantoin

X,Y = H or CH_2OH

MMDMH
MMY

Molecular weight	DMY: 188.18, MMY: 158.16
Registration number	**Purity of the technical grade active ingredient**
25753	DMY: 45.0%, MMY: 10%
25756	DMY: 93.3%, MMY: 6.0%

2.2 Physical and chemical properties

Property	Result
Vapour pressure at 25°C	0.01 mPa (DMY)
Ultraviolet (UV) / visible spectrum	No absorbance at $\lambda > 300$ nm
Solubility in water	DMY 1770 g/L MMY 833 g/L
n-Octanol/water partition coefficient	Log K_{ow} = -2.9 (DMY)
Dissociation constant	pKa_1 = 13.42 (DMY)

3.0 Impact on human health and animal health

3.1 Toxicology summary

The hydantoins, 1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin (DMY) and hydroxymethyl-5,5-dimethylhydantoin (MMY), are comprised of a dimethylhydantoin (DMH) carrier bound to either one (mono-, MMY) or two (bis-, DMY) hydroxymethyl functional groups. Upon interaction with water, the hydroxymethyl moieties are hydrolyzed to release formaldehyde, the biocidal moiety, and DMH, which is the major degradate. In the aqueous state, these compounds exist in a steady state equilibrium, with the majority of the total formaldehyde content bound to the hydantoin carrier with very low amounts existing as free formaldehyde.

A detailed review of the toxicology database for the hydantoins was conducted by the PMRA. The database for DMY and MMY is limited, consisting of acute toxicity, short-term toxicity and genotoxicity studies, and is presented in Appendix III, Table 3. The available toxicity studies were conducted with test material comprised of both DMY and MMY ranging from 33.2% DMY/31.5% MMY, up to 91.8% DMY/0.4% MMY. Given the hydrolysis of DMY/MMY to DMH and formaldehyde, these degradates were the focus of the hazard assessment for DMY/MMY. A full array of toxicity studies currently required for hazard assessment, with the exception of some acute toxicity studies, were available for DMH and are presented in Appendix III, Table 4. The available studies for DMY/MMY and DMH were carried out in accordance with accepted international testing protocols and Good Laboratory Practices. The hazard assessment also considered information found in the published literature. The formaldehyde assessment relied, in large part, on previous assessments undertaken by the Government of Canada and the United States Environmental Protection Agency (USEPA). The collective information was considered adequate to characterize the potential health hazards associated with DMY and MMY and their degradates.

DMY, MMY, DMH

When radiolabelled DMH was administered as a single low or high gavage dose to rats, it was rapidly absorbed from the gastrointestinal tract. Seven days post-dosing, radioactivity was absent in most tissues with the highest residual levels of radioactivity observed in hair. The majority of the administered radioactivity was recovered as unmetabolized DMH in the urine during the first 12 to 24 hours post-dosing. A minimal amount of the administered radioactivity was eliminated in the feces of rats. When DMH was administered in a repeat-dosing regimen in rats, the toxicokinetic profile was similar to that noted following the single-dose studies. In rabbits, orally-administered radiolabelled DMH was also rapidly absorbed, excreted and unmetabolized, primarily via the urine. Fecal excretion was a minor route of elimination. Small amounts of radioactivity were evenly distributed in the tissues at 72 hours post-dosing. No significant differences were noted between the sexes in the available toxicokinetic studies.

The hydantoins DMY/MMY were of low to slight acute toxicity via the oral route in rats, low acute toxicity via the dermal route in rabbits and low to moderate acute toxicity via the inhalation route of exposure in rats. DMY/MMY were minimally to slightly irritating to the skin and non- to moderately irritating to the eyes of rabbits. When tested in guinea pigs, DMY/MMY did not demonstrate any potential for dermal sensitization in a supplemental Buehler assay. Clinical

signs noted in acute toxicity studies at high dose levels included reddish stains around the eyes and muzzle, dirty hair coats, fecal stains, ataxia, salivation, piloerection, hunched posture, shallow and labored breathing and slight to severe depression. Severe clinical signs including ataxia, gasping of breathing, slight to severe depression and tremors, were observed only on the day of dosing in acute toxicity studies. The carrier molecule DMH was of low acute toxicity via the oral route when tested in mice and in a supplemental dog study. DMH was not a dermal sensitizer in guinea pigs in Buehler assays. Clinical signs noted immediately following dosing with DMH included lethargy, urogenital staining, ataxia and labored respiration in mice. No other acute toxicity studies conducted with DMH were available.

In a 90-day oral gavage toxicity study in rats, high dose levels of 45% DMY/10% MMY did not induce any clinical signs of toxicity, mortality or effects on body weight. The only treatment-related effect noted in this study was an increase in adrenal weight. The dermal administration of 45% DMY/10% MMY for 90 days to rabbits in a supplemental toxicity study resulted in severe irritation, including necrosis, ulceration with scab formation, fissures, exudation, thickening, discolouration and edema at the application site. Ulcerated tongue and lips, along with decreased body weight were also observed. In short-term repeat-dose oral toxicity studies conducted with DMH in mice, rats and dogs, limited treatment-related effects were noted. For DMH, treatment-related effects were mostly seen at dose levels equal to, or above, the limit dose level for testing of 1000 mg/kg bw/day. No consistent target organ was identified in the studies; however, pathological or weight changes of the adrenal gland and kidney were observed in a few studies. In the 90-day dermal toxicity study conducted with rats, DMH had no treatment-related effect on clinical signs of toxicity, body weight, hematology, clinical chemistry, gross or microscopic pathology, organ weights or signs of irritation at the highest dose level tested.

Long-term dietary toxicity studies with DMH in mice and rats were available. The treatment-related effects noted in mice and rats exposed to DMH included decreased body weight and hepatocellular necrosis. Also noted were hyperplasia of the submandibular lymph nodes and mineralization of the renal pelvis in rats and an increased incidence of amyloidosis in mice. Based on the results obtained, long-term repeat-dose exposure to DMH appeared to result in slightly increased toxicity when compared to the short-term toxicity studies; however, this could also be attributed to the wide dose selection in these studies. There was no evidence of carcinogenicity in mice or rats.

When tested in vitro for genotoxicity, 45% DMY/10% MMY was found to be genotoxic in the majority of studies. These positive results were obtained in the bacterial reverse mutation assay with strains TA98 and TA100, the mouse lymphoma forward mutation assay, as well as in the mammalian gene mutation assay. No in vivo genotoxicity studies were available for DMY/MMY. When tested in vitro, DMH was negative in a battery of bacterial reverse mutation and mouse lymphoma forward mutation assays. In vitro exposure to DMH did not result in the induction of chromosome aberrations in Chinese hamster ovary cells, in unscheduled DNA synthesis in rat hepatocytes or in an increase in foci in the cell transformation assay. Following in vivo exposure to DMH, assays conducted with rats were also negative for chromosomal aberrations in bone marrow cells. It is possible that the positive genotoxicity results with DMY/MMY may be attributable to the release of formaldehyde, which has demonstrated genotoxic potential.

Two 2-generation reproductive toxicity studies with DMH were conducted in rats with comparable dose levels; one study was conducted via the diet whereas the other was conducted via gavage. In the dietary reproductive toxicity study, exposure to DMH resulted in a decrease in pup body weight and body weight gain at a dose level that exceeded the limit dose. Given that this dose level did not result in maternal or reproductive toxicity, the young appeared to be more sensitive to the effects of DMH as compared to adults. Similarly, in the reproductive toxicity study conducted by gavage, DMH resulted in decreased pup body weight in the absence of maternal toxicity. These effects were noted at a lower dose level than seen in the dietary study, also suggesting sensitivity of the young. At the high-dose level, decreased pup viability was noted in the F_2 generation, also in the absence of maternal toxicity. No reproductive toxicity was observed with the exception of a decrease in pup birth weight in the F_2 generation.

Developmental toxicity studies were available for rats and rabbits exposed to DMH by gavage. In a supplemental developmental toxicity study in rats, an increased incidence of skeletal variations (extra 14^{th} ribs) was noted in the absence of maternal toxicity; however, this study was limited by the fact that only the limit dose level was tested. In two other developmental toxicity studies in rats exposed to DMH, one of which was a supplemental range-finding study, no signs of developmental toxicity were noted at the limit dose level. In rabbits exposed to DMH in a supplemental developmental toxicity study, decreased fetal weight and an increase in post-implantation loss were noted in the absence of overt maternal toxicity at the limit dose, the only dose level tested. In another developmental toxicity study in rabbits, maternal toxicity was observed while no treatment-related effect was noted on fetal survival, weight or development up to the limit dose level. In the third gavage developmental toxicity study in rabbits exposed to DMH, vertebral and rib variations occurred in fetuses at dose levels that did not induce toxicity in maternal animals. At the limit dose level, slightly increased incidences of heart and/or great vessel defects and adactyly/brachydactyly were noted in fetuses, while body weight loss, decreased body weight gain and food consumption along with decreased gravid uterine weight were noted in maternal animals.

Formaldehyde

No toxicology data were provided by the registrant for formaldehyde. Consequently, Health Canada's PMRA consulted the Government of Canada's Priority Substances List (PSL) Assessment of formaldehyde conducted jointly by Health Canada and Environment Canada under the authority of the *Canadian Environmental Protection Act* (PMRA# 2973553) as well as the USEPA's Chemical Assessment Summary reported in the Integrated Risk Information System (IRIS) (PMRA# 2973569) for hazard and risk information. The following key information was obtained from the above-noted assessments and the *Pest Control Products Act* hazard characterization regarding potential pre- and post-natal toxicity was taken into consideration.

Since formaldehyde is water soluble, highly reactive with biological macromolecules and rapidly metabolized, adverse effects resulting from exposure are observed primarily in those tissues or organs with which formaldehyde first comes into contact. That is, the respiratory tract following inhalation and the gastrointestinal tract following ingestion. In acute toxicity studies, formaldehyde was moderately toxic to rats via the oral and inhalation routes of exposure. Formaldehyde demonstrates irritant and dermal sensitization potential. In available studies,

formaldehyde did not affect reproduction or development at levels of exposure lower than those associated with adverse health effects at the site of contact. Formaldehyde is weakly genotoxic, with effects most likely to be observed in vivo in cells from tissues and organs with which the aldehyde first comes into contact. Following long-term inhalation exposure, formaldehyde also produced nasal squamous cell carcinomas in rats.

The toxicology reference values for use in the human health risk assessment of DMY/MMY are summarized in Appendix III, Table 1. Toxicology reference values for formaldehyde are summarized in Appendix III, Table 2. Results of the toxicology studies conducted on laboratory animals with the hydantoins (DMY/MMY) and the carrier molecule DMH, are summarized in Appendix III, Tables 3 and 4, respectively.

Epidemiology – DMY, MMY, DMH

A number of studies, either submitted by the registrant or in the published literature, investigated the dermal irritation and sensitization potential of the hydantoins in humans (PMRA# 2849774, 2849775, 2849776, 2849777, 2849779, 2849780 and 2849781). These studies presented data collected from different countries spanning the 1980s up to 2012.

In studies conducted in the 1980s, the sensitization potential of DMY, MMY and DMH was investigated in the Netherlands in 35 patients known to be allergic to formaldehyde (PMRA# 2849776). Of the patients allergic to formaldehyde, no patients reacted to DMH. Of the 14 patients sensitive to formaldehyde that were tested with DMY, eight had positive patch test reactions. Of the 21 patients tested with MMY, seven reacted to MMY. Based on the results of this study, it appeared as though patients with an allergy to formaldehyde could also display a dermal reaction to DMY and MMY but not to DMH.

When DMY was patch tested as a 2.0% petrolatum test preparation in German patients between 1990 and 1994, four positive and 14 possible irritative reactions were noted in the 1374 people tested (PMRA# 2849775). This study demonstrated a low sensitizing potency for DMY. When DMY was patch tested in 2.0% petrolatum in 34 321 patients or in 2.0% aqueous solution in 1808 patients in Germany between January 1994 and December 2000, the proportion of positive reactions ranged from 0.39% to 0.65% (PMRA# 2849774). A retrospective study examined DMY as a 2.0% aqueous solution in 1946 adults (1283 women and 663 men) between January, 2006 and December, 2008 in Denmark (PMRA# 2849777). Positive reactions were noted in less than 1.0% of men and women. In a retrospective study conducted between January 2005 and December 2009 in six Spanish hospitals, DMY was tested as a 2.0% aqueous solution (PMRA# 2849780). DMY was patch tested in 1163 patients and induced a positive response in 10 patients. Half of the 10 patients who were allergic to DMY also reacted to formaldehyde. The North American Contact Dermatitis Group conducted patch tests between January, 2011 and December, 2012. DMY was administered as a 1.0% solution in petrolatum and the results obtained indicated that 67 positives were noted out of 4232 patients in 2011 to 2012. These results (using 1.0% solution) were compared with the pooled prevalence rates for the previous decade (2001 to 2010). This comparison revealed that DMY had statistically lower rates of positive patch tests in 2011 to 2012 as compared to these pooled prevalence rates (PMRA# 2849779); however, using a 1.0% solution instead of a 2.0% solution might have had an impact on these results.

DMY was patch tested at 1.0% concentration in both an aqueous and a petrolatum-based vehicle from 1992 to 2004 (PMRA# 2849781). The petrolatum-based allergen preparation induced more positive reactions than the aqueous allergen in almost every 2-year period. Of the total 845 positive-responders to DMY, 30% were sensitive to only the aqueous-based preparation and 44% were sensitive to only the petrolatum-based preparation; 23% were sensitive to both preparations. DMY petrolatum positive patients were more likely to be formaldehyde sensitive. The results of this study found that most patients (83%) who are allergic to DMY are also reactive to formaldehyde yet only 17 to 21% of formaldehyde-allergic patients were reactive to DMY. Of note, the study authors indicated that the 1.0% DMY preparation would release 200 ppm formaldehyde in the patch test; this value is lower than the stated elicitation threshold of 250 ppm for formaldehyde.

The dermal photosensitization potential of a 55% aqueous solution of DMY at a concentration of 4000 ppm was studied in 25 human subjects (12 males, 13 females) (PMRA# 2849758). DMY did not induce phototoxic or photoallergic reactions in any of the subjects during the study. The photoallergic potential of a skin lotion containing 0.25% DMY was evaluated in 30 subjects (5 males, 25 females) ranging in age from 19 to 63 years (PMRA# 2849758). The test substance did not induce photoallergic reactions and only slight transient reactions of erythema were noted during the study.

Overall, the results of these studies demonstrated that the hydantoins, when tested at varying concentrations, have the potential to induce dermal irritation and sensitization at a low incidence in the human population. It is unclear whether release of formaldehyde from DMY/MMY or cross-reactivity with formaldehyde is a contributing factor in sensitive individuals.

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.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, no developmental or reproductive toxicity studies were available for DMY/MMY. However, two multi-generation reproductive toxicity studies in rats (one dietary, one gavage) and gavage developmental toxicity studies in rats and rabbits were available for DMH.

With respect to pre- and postnatal toxicity, sensitivity of the young was investigated in numerous rat and rabbit developmental toxicity studies. In a supplemental developmental toxicity study in rats, an increased incidence of skeletal variations (extra 14^{th} ribs) was noted in the absence of overt maternal toxicity at the limit dose level, the only dose level tested. In the other developmental toxicity studies in rats exposed to DMH, no signs of developmental toxicity were noted at the limit dose level. In pregnant rabbits exposed to DMH in a supplemental developmental toxicity study, decreased fetal weight and an increase in post-implantation loss were noted in the absence of maternal toxicity at the limit dose level, the only dose level tested. In another developmental toxicity in rabbits, no developmental toxicity was noted at the limit

dose level, in the presence of maternal toxicity. In a third gavage developmental toxicity study in rabbits exposed to DMH, variations occurred at dose levels that did not induce toxicity in maternal animals. At the limit dose level, a slightly increased incidence of malformations was noted in fetuses in the presence of maternal toxicity. In both of the two available 2-generation reproductive toxicity studies in rats exposed to DMH, decreased pup weight was observed in the absence of maternal toxicity. In one of the reproductive toxicity studies, administration of DMH at a limit dose level resulted in a slight decrease in pup viability in the F_2 generation in the absence of maternal toxicity.

Overall, the toxicology database is adequate for determining the sensitivity of the young, as all required studies were available for DMH, the degradate of DMY/MMY. Sensitivity of the young was identified in the rat reproductive as well as in the rat and rabbit developmental toxicity studies conducted with DMH. The treatment-related effects at the LOAEL in these studies were not considered serious in nature. When the selected endpoint for the risk assessment of the hydantoins was derived from the rabbit developmental toxicity study (increased fetal variations in the absence of maternal toxicity), the *Pest Control Products Act* factor (PCPA factor) was reduced to threefold to address residual concerns for potential sensitivity of the young. However, when the endpoint from the rat reproductive toxicity study (reduced pup weight in the absence of maternal toxicity) was used in the risk assessment, the PCPA factor was reduced to 1-fold on the basis of a lower degree of concern for the endpoint. *Pest Control Products Act* considerations for formaldehyde are presented in Section 3.3.1.2.

3.2 Dietary exposure and risk assessment

There are no food uses associated with the preservative uses of DMY/MMY. Residues of DMY/MMY in potential drinking water sources are not anticipated as a result of the preservative uses. Therefore, no dietary exposure is anticipated.

3.3 Occupational and non-occupational risk assessment

Occupational and non-occupational (for example, residential) risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

3.3.1 Toxicology reference values

3.3.1.1 Toxicology reference values for occupational and non-occupational exposure to DMY/MMY (based on the degradate DMH)

Short-, intermediate, and long-term dermal and inhalation exposure:

For short-, intermediate- and long-term exposures via the dermal and inhalation routes, a developmental no observed adverse effect level (NOAEL) of 100 mg/kg bw/day from the rabbit oral developmental toxicity study with DMH was selected. At the lowest observed adverse effect level (LOAEL), developmental toxicity was observed in this study as an increased incidence of

skeletal variations in the absence of maternal toxicity. The available 90-day dermal toxicity studies did not assess the relevant endpoints of concern (developmental effects in the young following prenatal and/or postnatal exposure) and a repeat-exposure inhalation toxicity study was unavailable, thus necessitating the use of an oral study.

For residential scenarios, the target margin of exposure (MOE) selected for this endpoint is 300. Tenfold factors were applied each for interspecies extrapolation and intraspecies variability. As outlined in the *Pest Control Products Act* hazard characterization Section, the PCPA factor was reduced to threefold. The selection of this study and target MOE is considered to be protective of all populations including nursing infants and the unborn children of female workers.

For occupational scenarios, the target MOE for this endpoint is 300. Tenfold factors were applied each for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of concerns regarding prenatal toxicity (as outlined in the *Pest Control Products Act* hazard characterization Section), an additional threefold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females 13–49 years of age.

Dermal absorption

Rat in vivo dermal absorption studies for DMY and DMH were on file (PMRA# 1130130, 1130128, 2877043), and were re-examined to ensure current policies and standards were met. No dermal absorption data were submitted to PMRA or available in the published literature for MMY.

Dermal absorption values of 33% for DMH and 45% for DMY were determined based on the available data. A 50% dermal absorption value was selected for MMY based on a weight-of-evidence analysis of physical/chemical properties as well as the DMY rat in vivo dermal absorption study, given some MMY is expected to present in the test solution.

It is not possible to use a specific dermal absorption value for DMY, MMY or DMH alone in the exposure calculations, as these compounds exist in an equilibrium in aqueous solutions and their proportion will change over time as formaldehyde is released. A dermal absorption value of 50% was selected to address the absorption of all three chemicals through the skin from consumer products as well as the absorption of DMY and MMY from end-use products. Although the selected dermal absorption value may be conservative, it could not be further refined based on the currently available data.

Cancer assessment

In studies conducted with DMH, there was no evidence of oncogenicity in mice or rats, and as a result, a cancer risk assessment was not required for DMY, MMY, or DMH.

3.3.1.2 Toxicology reference values for occupational and non-occupational exposure to formaldehyde

Dermal

The Government of Canada's PSL assessment indicated that dermal exposure to concentrations of formaldehyde in the vicinity of 1–2% (10 000 to 20 000 ppm) is likely to cause skin irritation; in hypersensitive individuals, contact dermatitis can occur with concentrations as low as 0.003% (30 ppm). Given that formaldehyde exerts toxicity primarily through site-of-contact activity, no reference value was established by Health Canada's PMRA for systemic toxicity resulting from dermal exposure; irritant concentrations were considered qualitatively.

Short- and intermediate-term inhalation

Throughout the Canadian PSL assessment of formaldehyde, a no observed adverse effect concentration (NOAEC) of 1.2 mg/m^3 was consistently established in rats (mostly of the Wistar strain) in short-term repeat-dose inhalation toxicity studies. The NOAEC of 1.2 mg/m^3 was established in a 3-day inhalation toxicity study, in three 13-week inhalation toxicity studies, in one 3-month inhalation toxicity study with a 25-month recovery period, and in a 26-week inhalation toxicity study. A NOAEC of 1.2 mg/m^3 was also established in a 26-week inhalation toxicity study in cynomolgus monkeys. These NOAECs were based on histopathological effects and increased cell proliferation in the nasal cavity at concentrations of greater than, or equal to, 3.6 mg/m^3. Health Canada's PMRA selected this NOAEC of 1.2 mg/m^3 (equivalent to 0.33 mg/kg bw/day) for short- and intermediate-term risk assessment with standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For non-occupational scenarios, the PCPA factor was reduced to onefold, given that site-of-contact effects are the most sensitive endpoints and are not likely to be age-dependent. Thus, the target MOE is 100.

Long-term inhalation

The lowest point of departure established in the Canadian PSL assessment for chronic inhalation toxicity studies with formaldehyde was noted in a study conducted with F344 rats (PMRA# 2977582). In this study, rats were exposed to 0, 0.3, 2.17 or 14.85 ppm (equivalent to 0, 0.4, 2.6 or 17.8 mg/m^3) formaldehyde for 6 hours/day, 5 days/week for up to 28 months. The NOAEC was set at 0.4 mg/m^3 (equivalent to 0.11 mg/kg bw/day) with a corresponding LOAEC of 2.6 mg/m^3 based on histopathological effects in the nasal cavity. It should be noted that the incidence was summed for all animals examined during interim and terminal sacrifices. Health Canada's PMRA selected this NOAEC for long-term risk assessment with standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For non-occupational scenarios, the PCPA factor was reduced to onefold, given that site-of-contact effects are the most sensitive endpoints and are not likely to be age-dependent. Thus, the target MOE is 100.

Cancer assessment

Neither the Government of Canada's PSL assessment nor the USEPA review indicated a concern for potential carcinogenicity of formaldehyde via the oral or dermal route based on the available data.

For the inhalation route of exposure, in addition to degenerative, non-neoplastic effects of the nasal tissues, long-term inhalation exposure to formaldehyde produced nasal squamous cell carcinomas in both sexes of two strains of rats. Sustained cellular proliferation, as well as interaction with genetic material, likely contributes to induction of these tumours and under similar conditions, formaldehyde is considered to present a carcinogenic hazard to humans via inhalation. In the USEPA assessment, a 24-month inhalation study (PMRA# 2977583) was used for the determination of carcinogenic potency. In this study, Fischer 344 rats were exposed via inhalation to formaldehyde at 0, 2, 5.6 or 14.3 ppm (equivalent to 0, 2.46, 6.88 or 17.56 mg/m^3), 6 hours/day, 5 days/week for 24 months. In their analysis, the USEPA excluded animals that died prior to the appearance of the first squamous cell carcinoma as they were not considered at risk. Those animals sacrificed at 12 and 18 months were treated as though they would have responded in the same proportion as rats remaining alive at the respective sacrifice times and those living beyond 24 months were included with animals sacrificed at 24 months. From the estimates of the probability of death with tumour within 24 months and its variance, the number of animals at risk and the number with tumours were derived for a 24-month study with no 12- or 18-month kills. Based on this, the USEPA conducted a linear low-dose extrapolation on the following tumour response: 0/156, 0/159, 2/153, and 94/140 at respective concentrations of 0, 2.46, 6.88 and 17.56 mg/m^3. A unit risk of 1.3×10^{-5} $(\mu g/m^3)^{-1}$ was estimated by the USEPA.

In the Canadian PSL assessment, a study generated after the conduct of the USEPA review was used for the quantitative cancer assessment. In this study (PMRA# 2977584), male Fischer 344 rats were exposed to formaldehyde via the inhalation route at 0, 0.7, 2, 6, 10 or 15 ppm (equivalent to 0, 0.8, 2.4, 7.2, 12 or 18 mg/m^3) for 6 hours/day, 5 days/week for 24 months. The overall incidence of nasal squamous cell carcinoma at 0, 0.8, 2.4, 7.2, 12 or 18 mg/m^3 was 0/90, 0/90, 0/90, 1/90, 20/90 or 69/147. In the Canadian PSL assessment, a Tumorigenic $Concentration_{05}$ (concentration associated with a 5% increase in tumour incidence over background) was generated. However, to allow for comparison with the 24-month study where rats were exposed to formaldehyde by inhalation at 0, 2, 5.6 or 14.3 ppm (PMRA# 2977583), Health Canada's PMRA estimated a unit risk of 4.25×10^{-5} $(\mu g/m^3)^{-1}$ (equivalent to 1.69×10^{-1} $(mg/kg\ bw/day)^{-1}$ from the 24-month inhalation study in rats (PMRA# 2977584). Although the unit risks derived by the United States and Canada are similar, the data presented in PMRA# 2977584 (rather than PMRA# 2977583) provided a better concentration-response for modelling and thus, was used by Health Canada's PMRA to assess cancer risk from inhalation exposure only.

3.3.2 Non-occupational exposure and risk assessment

Non-occupational (residential) risk assessment involves estimating risks to the general population, including adults, youth, and children, during or after pesticide application.

3.3.2.1 Residential applicator exposure and risk assessment

A residential applicator assessment for the DMY/MMY preservative itself was not required since there are no registered domestic-class pesticide products. A residential applicator assessment was conducted for handling consumer products preserved with DMY/MMY.

Residential handlers are adults (>16 years old) who purchase consumer products containing DMY/MMY as a preservative. They are assumed to wear shorts, short-sleeved shirts, shoes, and socks. Exposures to painters and cleaners were used as the index exposure scenarios, as DMY/MMY is registered for use in polymer emulsions that may be formulated into paint as well as many cleaning products. These index scenarios are considered to address residential handler exposure for all other consumer products containing DMY/MMY as a preservative.

DMH

DMH was chosen as the representative chemical for the DMY, MMY, and DMH risk assessments as it is the degradate of DMY and MMY and the toxicology reference values were determined for DMH (see Section 3.1). Label end-use commercial-class product rates of DMY and MMY were converted into a DMH-equivalent rate (Appendix IV, Table 1). These are the rates for products manufactured at an industrial facility (such as polymer emulsions), which are typically precursor or intermediary products that may be further used in the manufacturing of consumer products (such as paint, cleaning products). The concentration of DMY and MMY in the final products sold to consumers is unknown; however, it is expected to be considerably less than the label end-use commercial-class product (manufacturing) rates, as DMY and MMY concentrations would be further diluted by other ingredients used in the formulation of these products.

There is potential for short- to long-term exposure to DMH when applying products preserved with DMY/MMY. The following scenarios were addressed:

- Applying paint using an airless sprayer;
- Applying paint using a brush/roller;
- Applying paint using an aerosol can;
- Cleaning using a mop, including pouring the cleaning solution into the mop container;
- Cleaning using ready-to-use (RTU) wipes;
- Cleaning using a RTU trigger spray bottle + wipe;
- Cleaning with a trigger spray bottle + wipe, including pouring the solution into the trigger spray bottle

Chemical-specific exposure data were not available for DMH for the painting or cleaning scenarios. However, a brush and roller study (PMRA# 2849401), an airless sprayer study (PMRA# 3003682), a liquid pour study (PMRA# 2296582), a mop study (PMRA# 2169144) and

a wipe study (PMRA# 2169213) were submitted by the Antimicrobial Exposure Assessment Task Force II (AEATF II). The primary purpose of the AEATF was to generate exposure data to support registration and re-registration of antimicrobial active ingredients. While there are limitations in the use of generic data, these exposure data represent the most reliable information currently available. Unit exposures for the aerosol can scenario are from Section 10: Treated Paints and Preservatives of the USEPA 2012 Residential SOPs (PMRA# 2409268). The aerosol can painting scenario would address exposure to any aerosol can household consumer product that may be preserved with DMY/MMY (such as, cleaners, air fresheners).

Dermal and inhalation unit exposure values from these studies were combined with the standard amounts of paint handled per day from the USEPA 2012 Residential SOPs (Section 10: Treated Paints and Preservatives) (PMRA# 2409268) and standard amount of cleaning solution from the USEPA Antimicrobial Division Residential SOPs (PMRA# 3120537).

For dermal and inhalation exposure to DMH from the use of consumer products containing DMY/MMY, the calculated MOEs are greater than the target MOEs for all residential handler scenarios except for painting with an airless sprayer at the maximum liquid end-use product (manufacturing) rate. As rates of DMY/MMY in the final consumer products are unknown, it is assumed that the concentrations of DMY/MMY would be considerably less than the rate used in the manufacturing of these products. Considering this conservatism, risks for all residential handler scenarios, including the airless sprayer, were determined to be acceptable. The residential handler non-cancer exposure and risk assessments for DMH can be found in Appendix IV, Table 2.

Formaldehyde

Formaldehyde is present in DMY/MMY products and can be released into the air during the hydrolysis of DMY/MMY to DMH. Therefore, there is potential exposure to formaldehyde from handling liquid consumer products containing DMY/MMY as a preservative. A quantitative assessment was not required for the dermal route, as no reference value was established by the PMRA for systemic toxicity resulting from dermal exposure and irritant concentrations were considered qualitatively (see Section 3.3.1.2).

In any liquid end-use or consumer DMY/MMY product, the majority of the total formaldehyde content is bound to the hydantoin carrier with very low amounts existing as free formaldehyde. Volatilization of free formaldehyde molecules are the main source of airborne formaldehyde, as data indicates that aerosol mists were only a minor contributor to formaldehyde air concentrations (PMRA# 2877043).

Algorithms were used to estimate the air concentration of formaldehyde from the concentration of aqueous free formaldehyde and the temperature of the solution (PMRA# 2877043, 3244217). The concentration of aqueous free formaldehyde in DMY/MMY products available for volatilization (Appendix IV, Table 3) was determined from the maximum DMH-equivalent manufacturing product label rate and assumed the PMRA's maximum acceptable level of free formaldehyde (1%) for all products. The air concentration corresponding to the aqueous free formaldehyde was then calculated (Appendix IV, Table 4). The resulting formaldehyde air concentration value of 0.004 ppm was used to calculate inhalation exposure when handling end-

use and consumer products. This calculated air concentration is considered to be conservative as free formaldehyde levels in end-use products are lower than 1% and these manufacturing products are further diluted in the formulation of consumer products. The equations also assume that formaldehyde vapour would reach equilibrium, which is unlikely in a manufacturing facility or consumer scenario where there is a constant exchange of air.

There is confidence in the air concentration equations, as there was a good correlation of calculated and measured airborne levels of formaldehyde in the underlying study (PMRA# 2877043). Although this study was conducted in a metalworking shop using a different active ingredient, the assumptions underlying the equations are based on formaldehyde and are not related to the source compound or use scenario.

The estimated formaldehyde air concentration value was combined with exposure time (3 hours), as well as the standard light inhalation rate and body weight from the USEPA Residential SOPs (PMRA# 2409268) to estimate exposure. The 3 hour exposure time was based on the total time spent painting and addresses time spent handling other consumer products preserved with DMY/MMY. For the cancer assessment, the standard treatment frequency of 30 days was assumed. It was also assumed that a person would handle a consumer product containing DMY/MMY each year of their adult life (63 years) over a lifetime of 78 years (PMRA# 2409268).

For residential handler inhalation exposure to formaldehyde from the use of consumer products containing DMY/MMY as a preservative, the inhalation MOEs were greater than the target MOE and risks were shown to be acceptable. The residential handler inhalation non-cancer exposure and risk assessment for formaldehyde is presented in Appendix IV, Table 5.

The cancer risks to formaldehyde for residential handlers was estimated to be 2×10^{-6}. This cancer risk was slightly greater than 1×10^{-6} but considered acceptable due to conservatisms in the assessment. These conservatisms include the assumption of a 1% amount of free formaldehyde in consumer products as well as the use of the maximum end-use product (manufacturing) rates to calculate risks to consumer products. The rates of active ingredient in consumer products are unknown, but are likely to be much lower as manufacturing products are diluted in the formulation of consumer products. The residential handler inhalation cancer exposure and risk assessment for formaldehyde is presented in Appendix IV, Table 6.

3.3.2.2 Residential postapplication exposure and risk assessment

Residential postapplication exposure occurs when an individual is exposed through dermal, inhalation and/or incidental oral (non-dietary ingestion) routes as a result of being in a residential environment where a consumer product containing DMY/MMY (and subsequently formaldehyde) as a preservative has been used.

A quantitative residential postapplication assessment was not conducted for consumer products due to the uncertainty associated with these scenarios. This includes uncertainty regarding the concentration of the active ingredient rates in consumer products, and uncertainty regarding standard assessment values (such as the amount of product film remaining on skin or surfaces, transferable residues, amount handled). Although some of this information is available for pesticides, there was uncertainty whether it would be representative of a preservative scenario.

Considering the above, the end-use product maximum (manufacturing) rates and sentinel exposure scenarios (residential handler) were used to qualitatively assess postapplication exposure following application of consumer products containing DMY/MMY (and subsequently formaldehyde) as a preservative, and were considered acceptable. While there are uncertainties with this approach due to the potential range of downstream consumer products and exposure to various sub-populations, postapplication exposure and risk are not expected to be of concern given that risks for all residential handler scenarios for DMH (3.3.2.1) and formaldehyde (3.3.2.1), were determined to be acceptable.

3.3.3 Occupational exposure and risk assessment

There is potential for exposure in occupational scenarios when workers handle DMY/MMY end-use products during the mixing and loading process in industrial (manufacturing) settings (primary handlers) and when workers handle consumer products treated with DMY/MMY as a preservative (secondary handlers).

3.3.3.1 Occupational primary handler (manufacturing) exposure and risk assessment

There is potential for exposure when workers mix and load DMY/MMY end-use products during the manufacturing process of a wide range of consumer products.

DMH

As discussed in Section 3.3.2.1, DMH was chosen as the representative chemical for the DMY, MMY, and DMH risk assessments as it is the degradate of DMY and MMY and toxicology reference values were determined for DMH (see Section 3.1). Label end-use product rates of DMY and MMY were converted into a DMH-equivalent rate (Appendix IV, Table 1).

Primary handlers have the potential for short- to long-term exposure to DMH as work in the manufacturing facility could occur year-round. Based on the use pattern, the following scenarios were assessed:

- Manual mixing/transfer of liquids using conventional containers (liquid pour)
- Manual mixing/transfer of powders (solid pour)

The exposure estimates for primary handlers are based on different levels of personal protection equipment (PPE) and engineering controls:

- Single layer PPE: long-sleeved shirt, long pants, and chemical-resistant (CR) gloves
- Filtering facepiece respirator (dust mask)
- Closed transfer of liquids

No appropriate chemical-specific handler exposure data were available for DMY/MMY. Therefore, dermal and inhalation exposures for occupational applicators were estimated using the liquid pour (PMRA# 2296582, 2296584) and solid pour (PMRA# 2834812) exposure studies submitted by the AEATF II. While there are limitations in the use of generic data, these exposure data represent the most reliable information currently available. Inhalation exposures were based on light inhalation rates (17 L/min).

Dermal and inhalation unit exposure values from these studies were combined with the standard amounts of paint treated per day by workers in manufacturing facilities to estimate exposures. The amount of paint treated per day was based on the USEPA Antimicrobial Division Draft Summary of Amounts Handled or Treated for Occupational Handler Scenarios (PMRA# 3084493). The standard value for manufacturing paints was used as very little data is available regarding the typical amounts of product handled in the manufacturing of all potential products on the label. This primary handler assessment is expected to address exposure during the manufacturing process of all downstream registered products containing DMY/MMY as a preservative.

For the primary handler dermal and inhalation exposure to DMH from DMY/MMY end-use products, the combined MOEs were less than the target MOE for both the liquid pour and the solid pour scenarios at single layer PPE (long pants, long-sleeved shirt, and chemical resistant (CR) gloves). For the solid pour scenario, target MOEs were achieved and risks were shown to be acceptable with the addition of a filtering facepiece respirator (FFR) (dust mask), which is currently required on the label ("dust filtering respirator"). For the liquid pour scenario, risks could not be mitigated with additional PPE as the underlying AEATF study indicated that exposure was primarily to the hands and exposure to the remainder of the body was minimal. To mitigate exposure, it is proposed that closed transfer systems be used for handling the commercial-class liquid solution products. Results of the dermal and inhalation primary handler (manufacturing) risk assessments for DMH is found in Appendix IV, Table 7.

Formaldehyde

As discussed in Section 3.3.2.1, formaldehyde is present in DMY/MMY products and can be released into the air during the hydrolysis of DMY/MMY to DMH. Therefore, there is potential for short- to long-term exposure to formaldehyde from handling liquid end-use products containing DMY/MMY. A quantitative assessment was not required for the dermal route, as no reference value was established by the PMRA for systemic toxicity resulting from dermal exposure and irritant concentrations were considered qualitatively (see Section 3.3.1.2).

The air concentration of formaldehyde from volatilization of free formaldehyde from liquid end-use products was estimated to be 0.004 ppm. This air concentration was calculated using formaldehyde-specific algorithms and conservative assumptions, such as the maximum end-use product rate. Refer to Section 3.3.2 for more information.

The estimated formaldehyde air concentration value was combined with a standard 8 hour workday, as well as the standard light inhalation rate and body weight (80 kg) to estimate exposure. For the cancer assessment, it was assumed that a worker would handle a DMY/MMY end-use product every workday of the year, except when on vacation (250 days per year). It was also assumed that a worker would handle a consumer product containing DMY/MMY each year of their working career (40 years) over a lifetime of 78 years. The working career was based on the standard assumption for agricultural pesticides and is considered conservative for workers in industrial (manufacturing) facilities.

For primary handler inhalation exposure to formaldehyde from DMY/MMY end-use products, the inhalation MOEs were greater than the target MOE and risks were shown to be acceptable. The formaldehyde inhalation non-cancer exposure and risk assessment is presented in Appendix IV, Table 8.

The cancer risk for primary handlers was 3×10^{-5}. This cancer risk was greater than 1×10^{-5} but was considered acceptable due to conservatisms in the assessment. These include the assumption of a 1% amount of free formaldehyde in consumer products as well as the use of the maximum end-use product (manufacturing) rate. The formaldehyde inhalation cancer exposure and risk assessment is presented in Appendix IV, Table 9.

3.3.3.2 Occupational secondary handler exposure and risk assessment

Occupational secondary handlers include workers in facilities that manufacture consumer products and professionals who may handle consumer products, such as paint or cleaning products.

Downstream workers in manufacturing facilities

Downstream workers in industrial (manufacturing) settings are expected to be wearing PPE as required by provincial or territorial occupational health and safety standards, which would limit potential exposure. Therefore, a quantitative risk assessment for downstream workers in industrial facilities involved with the manufacturing of consumer products containing DMY/MMY as a preservative was not conducted and was instead considered qualitatively.

Secondary handlers using consumer products

There is potential for occupational exposure of professional secondary handlers using consumer products containing DMY/MMY as a preservative. Exposures to painters and cleaners were used as the index exposure scenarios as DMY/MMY is registered for use in polymer emulsions (which may include paint) as well as many cleaning products. These index scenarios are considered to address occupational secondary handler exposure for all other consumer products containing DMY/MMY.

DMH

As discussed in Section 3.3.2.1, DMH was chosen as the representative chemical for the DMY, MMY and DMH risk assessments. DMH-equivalent end-use commercial-class product (manufacturing) rates were used (Appendix IV, Table 1). The concentration of DMY and MMY in consumer products (such as paint, cleaning products) is expected to be considerably less than the manufacturing rates as DMY and MMY concentrations would be further diluted by other ingredients used in the formulation of these products.

Secondary handlers have the potential for short- to long-term exposure to DMH as consumer products preserved with DMY/MMY could be used year-round. Based on the use pattern, the scenarios identified for the index exposure scenarios (paint, cleaning products) are:

- Applying paints using a paint brush and roller;
- Applying paints using an airless sprayer;
- Cleaning with a mop, including pouring the cleaning solution into the mop container;
- Cleaning with RTU wipes;
- Cleaning with RTU trigger spray bottle + wipes;
- Cleaning with a trigger spray bottle + wipe, including pouring the solution into the trigger spray bottle.

No appropriate chemical-specific handler exposure data were available for DMY/MMY. Therefore, dermal and inhalation exposures for occupational applicators were estimated using data from the AEATF II, as discussed in Section 3.3.2.

Dermal and inhalation unit exposure values from these studies were combined with the standard amounts of paint handled per day: 18.75 L per day using a brush and roller (2001 PMRA survey) and 120 L per day using an airless sprayer (PMRA # 2992785). The amounts of cleaning products per day was based on the USEPA Antimicrobial Division Draft Summary of Amounts Handled or Treated for Occupational Handler Scenarios (PMRA# 3084493).

For dermal and inhalation exposure to DMH from the use of consumer products containing DMY/MMY as a preservative, calculated MOEs were greater than the target MOE at single layer PPE (long pants, long-sleeved shirt, no gloves) and determined to be acceptable for all secondary handler scenarios except for painting with an airless sprayer at the maximum liquid end-use product (manufacturing) rate. Although rates of DMY/MMY in the final consumer products are unknown, it is assumed that the concentrations of DMY/MMY would be considerably less than the rate used in the manufacturing of these products. Considering this conservatism, the calculated MOEs for the airless sprayer were determined to be acceptable. The secondary handler non-cancer exposure and risk assessments for DMH can be found in Appendix IV, Table 10.

Formaldehyde

Non-cancer and cancer exposure and risks to formaldehyde for secondary handlers is addressed by the occupational primary handler assessment (see Section 3.3.3.1). The methods and inputs used to calculate non-cancer and cancer exposure are the same for both the primary and secondary handler scenarios. The estimated air concentration of formaldehyde was the same for both end-use and consumer products as the maximum end-use product rate was used.

As non-cancer and cancer inhalation risks to formaldehyde for primary handlers were acceptable (see Appendix IV, Tables 9 and 10), inhalation risks to formaldehyde for secondary handler exposure from consumer products preserved with DMY/MMY are also acceptable.

3.4 Aggregate risk assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures from the use of products containing DMY/MMY as a preservative. Additionally, only exposures from routes that share common toxicological endpoints can be aggregated.

There are no registered DMY/MMY food uses, nor is it in areas where food is stored, handled or processed. Residues of DMY/MMY in potential drinking water sources are not anticipated as a result of the preservative uses. Therefore, an aggregate exposure and risk assessment is not required.

A Letter of No Objection (LONO) for the use of DMY/MMY in food contact materials has not been issued. As such, it is proposed that labels be updated to prohibit the use of DMY/MMY in the manufacture of paper and paperboard that will come into contact with food.

3.5 Cumulative assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. Accordingly, an assessment of potential common mechanism of toxicity with other pesticides was undertaken for DMY/MMY. There are no available data to indicate that DMY/MMY has a common mechanism of toxicity with other pesticides. The DMH moiety of the hydantoins is present in other pesticides registered for use in Canada. As well, other formaldehyde-releasing pesticides are registered in Canada. Following the completion of the human health risk assessments of other formaldehyde-releasing or DMH-containing pesticides, it will be determined whether a cumulative risk assessment is necessary. If so, a cumulative risk assessment will be performed for all relevant chemicals of the cumulative assessment group(s) at that time.

3.6 Health incident reports

As of 25 January 2022, no human or domestic animal incidents involving DMY and/or MMY were submitted to the PMRA.

4.0 Environmental assessment

DMY and MMY are used as material preservatives in various products including liquid detergents, soft soaps, room deodorizers, polymer emulsions, water-based gels for household and industrial products, and textiles. The registered uses of these active ingredients are considered to be indoor industrial uses, therefore the potential for direct exposure to the environment from application is not expected. However, these active ingredients could enter the environment when present in the effluent discharge from industrial sites or wastewater treatment plants.

4.1 Fate and behaviour in the environment

DMY and MMY are likely to degrade rapidly via hydrolysis to 5,5-dimethylhydantoin (DMH) and formaldehyde. While DMH is stable to hydrolysis and phototransformation (PMRA# 3244211), formaldehyde is not likely to persist in water or soil (PMRA# 2996270).

4.2 Environmental risk characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur.

Registered uses of DMY and MMY are limited to preservation of materials (detergents, soaps, textiles and inks). Direct exposure of the environment from these uses is not expected.

The use of consumer products, such as liquid detergents and soft soaps, may results in presence of DMY and MMY in household wastewater. Environmental exposure to DMY, MMY, DMH and formaldehyde from the use of consumer products is expected to be low due to dilution and wastewater treatment. The USEPA (PMRA# 3244211) identified DMH as the moiety of concern due to rapid transformation of the parents. Ecotoxicity information available to the USEPA indicated that DMH demonstrates low toxicity to terrestrial and aquatic organisms. Risks to aquatic organisms are acceptable for registered uses of DMY and MMY due to expected low environmental exposure.

End-use product labels include a warning that the products are toxic to fish and aquatic invertebrates. An update to the label statement prohibiting effluent discharge is proposed. The proposed label updates are included in Appendix V.

5.0 Pest control product policy considerations

5.1 Assessment of DMY and MMY under the Toxic Substances Management Policy (TSMP)

In accordance with the PMRA Regulatory Directive DIR99-03,[3] the assessment of DMY and MMY against Track 1 criteria of Toxic Substances Management Policy (TSMP) under *Canadian Environmental Protection Act* was conducted. It determined that:

- DMY and MMY do not meet all Track 1 criteria, and are not considered Track 1 substances.
- DMY and MMY do not form any transformation products that meet all Track 1 criteria.

5.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[4] The list is used as described in the PMRA Notice of Intent NOI2005-01[5] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[6] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Based on the manufacturing process used, impurities of human health or environmental concern as identified in the Canada Gazette, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the technical grade products.

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3 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*.

4 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

5 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*.

6 DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

6.0 Value assessment

DMY and MMY are important for aiding in the prevention and control of bacterial and fungal contamination of aqueous-based materials. Such contaminations can lead to product failures of function or discolourations/unpleasant odours that will make the product unusable.

There are currently a large number of alternative preservative products based on many different active ingredients or combination of active ingredients registered for the same materials as DMY and MMY. These active ingredients cover a range of different modes of action, including other formaldehyde releasing compounds (for example, hexahydro-1,3,5-tris (2-hydroxyethyl)-s-triazine).

List of abbreviations

↑	increased
↓	decreased
♂	male
♀	female
µCi	microcurie
µg	microgram
AD	administered dose
ADD	absorbed daily dose
AEATF II	Antimicrobial Exposure Assessment Task Force II
AHPD	amount handled per day
a.i.	active ingredient
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aq	aqueous phase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CHO	Chinese hamster ovary
CH_2O	formaldehyde
CR	chemical-resistant
DA	dermal absorption
DMH	dimethylhydantoin
DMY	1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin
DNA	deoxyribonucleic acid
FFR	filtering facepiece respirator
F_1	first generation
F_2	second generation
fc	food consumption
g	gram(s)
GD	gestation day
GGT	Gamma-glutamyl transferase
HDT	highest dose tested
Hgb	hemoglobin
hr(s)	hour(s)
kg	kilogram(s)
L	litre(s)
LADD	lifetime absorbed daily dose
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest observed adverse effect level
LONO	Letter of No Objection
m^3	cubic meter
MAS	maximum average score
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume

max	maximum
mg	milligram(s)
min(s)	minute(s)
MIS	maximum irritation score
mL	millilitre(s)
MMY	hydroxymethyl-5,5-dimethylhydantoin
MOE	margin of exposure
mol	mole
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
PPE	personal protection equipment
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppm	parts per million
PSL	Priority Substances List
RBC	red blood cells
RTU	ready-to-use
sol	solution
SOP	Standard Operating Procedure
T	temperature
UE	unit exposure
USEPA	United States Environmental Protection Agency
WBC	white blood cells
wk	week
wt(s)	weight(s)
yr(s)	year(s)

Appendix I Registered products containing DMY and MMY in Canada

Table 1 Products containing DMY and MMY in Canada subject to proposed label amendments[1]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Active Ingredient (%)
25753	Technical Grade Active Ingredient	Arxada, LLC.	Glycoserve	Solution	DMY - 45 MMY - 10
25756			Dantogard XL-1000T	Solution	DMY - 93.3 MMY - 6.0
25939	Commercial		Dantogard XL-1000 Preservative	Soluble Powder	DMY - 93.3 MMY - 6.0
25754			Dantogard Preservative	Solution	DMY - 32.3 MMY - 7.2
25755			Glycoserve LAD	Solution	DMY - 45 MMY - 10.0
25757			Dantogard Plus Preservative	Soluble Powder	DMY - 88.6 MMY - 5.7 IPB – 5.0
27295		Troy Chemical Corporation	Mergal 395	Solution	DMY - 32 MMY - 7.5

IPB: 3-iodo-2-propynyl butyl carbamate

[1] as of 24 January 2022, excluding discontinued products or products with a submission for discontinuation

Appendix II Registered uses

Registered commercial class uses of DMY/MMY in Canada as of 24 January 2022.

Use Site Category	Active	Materials Preserved	Application Method and Equipment
18 - Materials	1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin (DMY) & Hydroxymethyl-5,5-dimethylhydantoin (MMY)	Liquid detergents, soft soaps, room deodorizers, air fresheners, water-based surfactants, polymer emulsions, protective and decorative coatings, water-based gels, textiles, water-based adhesives, latex for paper coatings and water-based inks	Directly incorporate in to the product formulation at the rate instructed.

Appendix III Toxicology reference values for health risk assessment

Table 1 Toxicology reference values for use in health risk assessment for DMY/MMY (based on the degradate DMH)

Exposure scenario	Study	Point of departure and endpoint	Target MOE[a]
Short, intermediate and long-term dermal[b]	Gavage developmental toxicity study - rabbits (DMH)	NOAEL = 100 mg/kg bw/day (↑ incidence of skeletal variations).	300
Short, intermediate and long-term inhalation[c]	Gavage developmental toxicity study - rabbits (DMH)	NOAEL = 100 mg/kg bw/day (↑ incidence of skeletal variations).	300
Cancer	A cancer risk assessment was not required for DMY, MMY, DMH.		

[a] MOE refers to a target margin of exposure for occupational and residential assessments
[b] Since an oral NOAEL was selected, a dermal absorption factor of 50% was used in route-to-route extrapolation.
[c] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 2 Toxicology reference values for formaldehyde

Exposure scenario	Study	Point of departure and endpoint	Target MOE[a]
Short- and intermediate-term inhalation	A variety of short- and intermediate-term repeat-dose inhalation toxicity studies - rats and monkeys	NOAEC = 1.2 mg/m^3 (~ 0.33 mg/kg bw/day) (histopathological effects and increased cell proliferation in the nasal cavity).	100
Long-term inhalation	28-month inhalation chronic toxicity/ oncogenicity study - rats	NOAEC = 0.4 mg/m^3 (~ 0.11 mg/kg bw/day) (histopathological effects in the nasal cavity)	100
Cancer	A q_1* of 4.25×10^{-5} (µg/m^3)$^{-1}$ (~1.69×10^{-1} (mg/kg bw/day)$^{-1}$) was calculated for the increased incidence of nasal squamous cell carcinoma in male rats exposed to formaldehyde via the inhalation route.		

[a] MOE refers to a target margin of exposure for occupational and residential assessments

Table 3 Toxicology profile for DMY/MMY

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted.

Study Type/Animal/ PMRA#	Study results
Acute oral (gavage) toxicity Rat (Sprague-Dawley) 91.8% DMY/0.4% MMY PMRA# 1123384	LD_{50} = 1900 mg/kg bw ♂/♀ All of the deaths occurred within the first day of dosing. Clinical signs of toxicity included fecal stains, a red discolouration around the muzzle, slight to severe depression, piloerection and animals were cool to the touch. Slight toxicity.
Acute oral (gavage) toxicity Rat (Sprague-Dawley)	LD_{50} > 2000 mg/kg bw ♂/♀ Clinical signs of toxicity included ataxia, salivation, fecal stains, piloerection,

Study Type/Animal/ PMRA#	Study results
33.2% DMY/31.5% MMY PMRA# 1197006	shallow and gasping breathing, slight to severe depression, reddish stains around eyes and on muzzle and dirty hair coats. Low toxicity.
Acute oral (gavage) toxicity Rat (Sprague-Dawley) 26.4% DMY/23.2% MMY PMRA# 1196985	LD_{50} > 2000 mg/kg bw ♂/♀ Clinical signs of toxicity included tremors in abdominal region, salivation, fecal stains, piloerection, shallow labored breathing, slight to severe depression, reddish stains around the eyes, on fur and on muzzle. Severe clinical signs observed only on the day of dosing. Low toxicity.
Acute dermal toxicity Rabbit (New Zealand White) 91.8% DMY/0.4% MMY PMRA# 1123385	LD_{50} > 2000 mg/kg bw ♂/♀ The only clinical signs of toxicity were congestion, nasal discharge and fecal stains in females. Skin reactions were characterized by marked to extreme erythema and edema, necrosis, desquamation and coriaceousness. Low toxicity.
Acute dermal toxicity Rabbit (New Zealand White) 33.2% DMY/31.5% MMY PMRA# 1197007	LD_{50} > 2000 mg/kg bw ♂/♀ Apart from dermal irritation at the dose site (erythema, edema and eschar), no signs of gross toxicity, abnormal behavior or necropsy findings at terminal sacrifice were observed. Low toxicity.
Acute dermal toxicity Rabbit (New Zealand White) 33.2% DMY/31.5% MMY PMRA# 1197008	LD_{50} > 2000 mg/kg bw ♂/♀ Clinical signs of toxicity included hunched posture, fecal stains and nasal discharge. Changes noted in the coloration or texture of the skin at the site of application included petechial, blanching, dark purple or dark brown discolouration, small scabbing on site, marked erythema, marked to extreme edema, slight to marked desquamation, slight to moderate coriaceousness and extreme necrosis. Low toxicity.
Acute dermal toxicity Rabbit (New Zealand White) 26.4% DMY/23.2% MMY PMRA# 1196986	LD_{50} > 2,000 mg/kg bw ♂/♀ Signs of irritation included erythema, edema, discolouration, blanching, desquamation, coriaceousness, petechial, necrosis and scabbing. Low toxicity.
Acute inhalation (whole body) toxicity Rat (Sprague-Dawley) 91.8% DMY/0.4% MMY PMRA# 1161407	LC_{50} > 2.05 mg/L ♂/♀ 2.05 mg/L: Clinical signs of toxicity included red ocular discharge, facial staining and test material on the fur (following exposure, until day 6), irregular/laboured breathing, hunched posture and lethargy (during exposure). Alopecia around the eyes, piloerection and reduced feces were noted on days 3 to 7 in most animals. All surviving animals had red discoloured lungs with an uneven surface/texture. Low toxicity.
Acute inhalation (whole body) toxicity Rat (Sprague-Dawley)	LC_{50} > 377.8 µg/L ♂/♀ Clinical signs of toxicity included alopecia, dried blood around eye and nose. Animals had reddened/darkened nasal turbinate tissues and ↓ bw.

Study Type/Animal/ PMRA#	Study results
45% DMY/10% MMY PMRA# 1130096	Moderate toxicity.
Acute inhalation (whole body) toxicity Rat (Sprague-Dawley) 33.2% DMY/31.5% MMY PMRA# 1197009	LC_{50} > 2.09 mg/L ♂/♀ Clinical signs of toxicity included ocular and nasal discharge, irregular respiration, dyspnea, gasping, hunched posture and hypoactivity (in exposure chamber with recovery noted within 1 hr after removal from chamber). Low toxicity.
Primary Dermal Irritation Rabbit (New Zealand White) 91.8% DMY/0.4% MMY PMRA# 1123388	Slightly irritating to the skin. MIS = 1.5 at 72 hrs MAS (24, 48, 72 hrs) = 1.17
Primary Dermal Irritation Rabbit (New Zealand White) 33.2% DMY/31.5% MMY PMRA# 1197013	Minimally irritating to the skin. MIS = 1.0 at 72 hrs MAS (24, 48, 72 hrs) = 0.11
Primary Dermal Irritation Rabbit (New Zealand White) 33.2% DMY/31.5% MMY PMRA# 1197012	Slightly irritating to the skin. MIS = 2.17 at 72 hrs MAS (24, 48, 72 hrs) = 0.94
Primary Dermal Irritation Rabbit (New Zealand White) 26.4% DMY/23.2% MMY PMRA# 1196990	Minimally irritating to the skin. MIS = 1.67 at 72 hrs MAS (24, 48, 72 hrs) = 0.5
Primary Eye Irritation Rabbit (New Zealand White) 91.8% DMY/0.4% MMY PMRA# 1123389	Moderately irritating to the eye. MIS = 18.33 at 72 hrs MAS (24, 48, 72 hrs) = 15.39
Primary Eye Irritation Rabbit (New Zealand White) 45% DMY/10% MMY PMRA# 1130094	Non-irritating to the eye. MIS = 0 at 72 hrs MAS (24, 48, 72 hrs) = 0
Primary Eye Irritation	Minimally irritating to the eye.

Study Type/Animal/ PMRA#	Study results
Rabbit (New Zealand White) 33.2% DMY/31.5% MMY PMRA# 1197010	MIS = 10 at 72 hrs MAS (24, 48, 72 hrs) = 3.56
Primary Eye Irritation Rabbit (New Zealand White) 33.2% DMY/31.5% MMY PMRA# 1197011	Minimally irritating to the eye. MIS = 11 at 72 hrs MAS (24, 48, 72 hrs) = 6.67
Primary Eye Irritation Rabbit (New Zealand White) 26.4% DMY/23.2% MMY PMRA# 1196989	Minimally irritating to the eye. MIS = 7.67 at 72 hrs MAS (24, 48, 72 hrs) = 3.44
Dermal Sensitization (Buehler method) Guinea Pig (Hartley Albino) 33.2% DMY/31.5% MMY PMRA# 1197014	Supplemental study due to limited group size. Negative for dermal sensitization.
90-day oral (gavage) toxicity Rat (Sprague-Dawley) 45% DMY/10% MMY PMRA# 1130104	NOAEL = 200-300 mg/kg bw/day (♂); 400–600 mg/kg bw/day (♀) 400–600 mg/kg bw/day: ↑ absolute adrenal gland wt; ↑ relative adrenal gland wt (♂). Note: dose levels increased after 9 wks of dosing.
90-day dermal toxicity Rabbit (New Zealand Albino) 45% DMY/10% MMY PMRA# 1130105	Supplemental study due to only one dosage level examined. 550 mg/kg bw/day: erythema, edema, desquamation and eschar formation (wk 2 onward), exfoliation (characterized by necrotic epidermis and dermis permeated by heterophils, wk 6 onward), ↓ bw (♂: wk 12 onward; ♀: wk 9 onward), necrosis, ulceration with scab formation, fissures, exudation, thickening, discolouration and edema at application site) and ulcerated tongue and lips.
Bacterial reverse mutation test *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and *Saccharomyces cerevisiae* D4 45% DMY/10% MMY PMRA# 1130108	Supplemental study as no replicates were performed. Negative with and without metabolic activation.
Bacterial reverse mutation test *Salmonella typhimurium* strains TA1535, TA1537, TA1538,	Positive in strains TA98 and TA100 with and without metabolic activation.

Study Type/Animal/ PMRA#	Study results
TA98 and TA100 45% DMY/10% MMY PMRA# 1130109	
Bacterial reverse mutation test *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 45% DMY/10% MMY PMRA# 1130110	Positive in strain TA98 without metabolic activation.
Mouse Lymphoma Forward Mutation Assay Mouse L5178Y cells 45% DMY/10% MMY PMRA# 1130116	Positive with and without metabolic activation.
Gene mutation in mammalian cells CHO cells 45% DMY/10% MMY PMRA# 1130119	Positive with and without metabolic activation.

Table 4 Toxicology profile for DMH (5,5-dimethylhydantoin)

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted.

Study type/ Species/Strain/ PMRA#	Doses/Purity	Study results
The absorption, distribution, metabolism, and excretion of DMH were investigated in rats and rabbits. PMRA# 2768305, 2768306 and 1171148 Rat: Single oral (gavage) dose of 104/104 or 1036/1043 mg/kg bw ♂/♀ Multiple oral (gavage) doses of 104/105 mg/kg bw ♂/♀, single radiolabeled dose on day 14 Single intravenous dose of 105/106 mg/kg bw ♂/♀ Oral: Absorption: radiolabeled DMH was rapidly absorbed. Distribution: detectable levels of radioactivity in the fur at 7 days post-dosing. Detectable levels of radioactivity were also present in the carcasses of both sexes and in the fat of 1♂ and 1♀ following a low-dose exposure. Males administered a high dose of radiolabeled DMH had higher detectable levels in their carcasses compared to ♀s. Following repeated dosing, detectable levels of radioactivity were higher in the carcasses of ♀; however, ♂ had		

Study type/ Species/Strain/ PMRA#	Doses/Purity	Study results
higher levels of radioactivity in fur compared to the levels found in ♀. Metabolism: Unmetabolized ^{14}C-DMH was the only residue found in the urine of both sexes and represented more than 90% of the administered dose (AD). The results demonstrated that dose, dose regime and sex had no effect on the metabolic profile. Excretion: more than 90% of the AD was excreted in the urine of both sexes; most excreted within 24 hrs post-dosing. Radioactivity was recovered from the feces (≤1.4% of the AD) during the 7 days following administration. Most of the radioactivity was recovered in the first 12 hrs of the study. Intravenous: Distribution: ♂ had higher detectable levels of radioactivity in the fur when compared to values for ♀. Detectable levels of radioactivity found in the carcass of ♀ were lower than the detectable levels found in ♂. Excretion: urinary excretion accounted for 95% of the AD in ♂ and 94% of the AD in ♀. Fecal recovery was 1.2% and 0.7% of the AD in ♂ and ♀, respectively during the 7 days following administration. Rabbit (New Zealand White): Single oral (gavage) dose of 200 µCi/animal of ^{14}C radiolabelled DMH Multiple oral (gavage) doses (♀ only) 30 µCi/animal of ^{14}C radiolabelled DMH Oral: Absorption: radioactivity was at a peak level in blood at 3 to 6 hrs post-dosing, steadily decreasing thereafter. The radioactivity in blood decreased in a non-linear fashion to background levels over the 72 hrs of observation with the data suggesting a half-life in blood of approximately 7 to 8 hrs. Distribution: radioactivity was evenly distributed among tissues 72 hrs post-dosing. Metabolism: only the unchanged parent compound was found in urine samples. Excretion: the principal route of excretion was via the urine with most of the recovered radioactivity (>85% of the AD) excreted in the first 36 hrs. Less than 2% of the AD was detected in the feces by 72 hrs. In total, over 98% of the AD was present in the combined urine and fecal samples.		
Acute oral (gavage) toxicity Mouse (CD-1) PMRA# 1141722	LD_{50} > 5000 mg/kg bw ♂/♀ Clinical signs of toxicity included lethargy, ataxia, labored respiration, prostration, hypothermia, lethargy and wet yellow urogenital staining. Low toxicity.	
Acute oral (capsule) toxicity Dog (Beagle) PMRA# 1141723	No mortalities up to 5000 mg/kg bw. Clinical signs of toxicity included emesis (study day 0), soft stool (study day 1) and hypoactivity (study day 0). Supplemental study due to limited group size.	
Dermal sensitization (Buehler method) Guinea Pig (Hartley Albino) PMRA# 1141726	Negative for dermal sensitization.	
Dermal sensitization (Buehler method) Guinea pig (Hartley derived) PMRA# 1229256	Negative for dermal sensitization.	

Study type/ Species/Strain/ PMRA#	Doses/Purity	Study results
28-day oral (dietary) toxicity Mouse (CD-1) PMRA# 1141714	NOAEL = 1643/2808 mg/kg bw/day ♂/♀ 11 106/14 860 mg/kg bw/day ♂/♀: ↓ bw (♂: wk 4; ♀: wk 1) and bwg (♂: wks 3 to 4; ♀: wks 0 to 1), slightly ↑ ALP; ↑ BUN (♀).	
90-day oral (dietary) toxicity Mouse (CD-1) PMRA# 1141717	NOAEL = 3339/4337 mg/kg bw/day ♂/♀ 8702/11 004 mg/kg bw/day ♂/♀: slightly ↓ bw (wks 11 to 12), ↓ WBC and cholesterol, slightly ↑ ALP and albumin, ↓ absolute brain wt (♂); slightly ↓ bwg (wks 0 to 1), ↑ WBC, RBC and Hgb, slightly ↑ AST, ↑ severity of lipid material in zone adjacent to the medulla in the cortex of the adrenal glands, ↑ liver and ovarian wts (♀).	
28-day range-finding oral (gavage) toxicity Rat (Sprague-Dawley) PMRA# 1141715	Supplemental study due to the design of the study and due to the lack of examination of hematology, serum chemistry, organ weights, gross and micropathology. ≥5000 mg/kg bw/day: ↑ incidence of dried red material around nose, eyes, chin and forearm (♂); ≥9000 mg/kg bw/day: ↑ incidence of lethargy and salivation; 12 500 mg/kg bw/day: ↓ fc (first wk of dosing); ↓ bw (wks 2 and 3) and bwg (wks 1 to 2) (♂); 2 mortalities (1♀ found dead on study day 1, 1 ♀ sacrificed moribund on study day 1), observations 1.5 hrs post-dosing in these animals included lethargy, ataxia, prostration, comatose with labored respiration, marked distension of the stomach noted at necropsy), fluid filled uterus at termination (2 survivors) (♀).	
90-day oral (gavage) toxicity Rat (Sprague-Dawley) PMRA# 1153695 and 1153696	NOAEL = 2000 mg/kg bw/day ≥5000 mg/kg bw/day: ↑ incidence of renal pelvic urolithiasis, slightly ↑ protein and RBC in urine; ↑ incidence of chronic interstitial nephritis (0, 2, 6 and 2), ↓ platelets (♂); 1 mortality (1♀ sacrificed moribund on study day 64), ↑ kidney and relative liver wts, ↓ absolute ovarian wt (♀); 10,000 mg/kg bw/day: salivation, ↑ BUN (12 wks), ALP and AST; 1 mortality (1♂ sacrificed moribund on study day 86), ↓ bw (wks 7 onward) and bwg (wks 2 to 3 and 6 to 7), ↑ cholesterol, ↓ absolute brain wt, ↑ relative liver wt (♂); ↓ platelets, ↑ albumin, ↑ absolute heart (♀).	
90-day oral (gavage) toxicity Rat (Sprague-Dawley) PMRA# 1239416	NOAEL = 300 mg/kg bw/day 1000 mg/kg bw/day: ↓ bw (wks 9 and 10), ↓ fc, ↓ liver wt (♂); ↑ liver and absolute kidney wts (♀).	
90-day oral (drinking water) toxicity Rat (Sprague-Dawley) PMRA# 1231780	NOAEL = 61/76 mg/kg bw/day ♂/♀ ≥629/764 mg/kg bw/day ♂/♀: ↓ absolute brain wt; ↑ AST, ↓ GGT, total protein (♂); ↑ phosphate, thickening of the adrenal cortical zona glomerulosa (2♀) (♀); 6578/7254 mg/kg bw/day ♂/♀: 13 mortalities (10♂ and 3♀; 6 were killed in extremis, 7 found dead), ↑ incidence of clinical signs of toxicity (thinness, emaciation, snout and urogenital staining), ↓ bw, fc and water intake, ↓ platelets, ↑ MCV, ↑ ALP, ALT, ↓ potassium, ↓ liver, absolute brain and absolute adrenal wts, ↑ relative brain and kidney wts, ↑ incidence of reduction/absence of fat pads, ↑ atrophy of the lymphoreticular system	

Study type/ Species/Strain/ PMRA#	Doses/Purity	Study results
	(thymus, spleen, lymph nodes), renal necrosis of the tip of the papilla, pelvic transitional cell hyperplasia, hyperplasia of the epithelium lining renal papilla, ↑ incidence of renal basophilic tubules, thickening of the adrenal cortical zona glomerulosa, ↓ cellularity of the bone marrow, ↑ number of animals with blood pigments in the urine; ↑ incidence of hunching, ↓ motor activity, ataxia and irritability, ↓ RBC, total plasma proteins and globulin fraction, ↑ Hgb and BUN, ↑ relative adrenal and testicular wts, ↓ absolute kidney and testicular wts (♂); ↑ AST, ↓ RBC (♀). Note: there was a wide range in dose levels due to high variation in water consumption throughout the study.	
7-day oral (capsule) toxicity Dog (Beagle) PMRA# 1141723	Supplemental study due to too few animals, only one dosage level tested and the capsule was retained by the 1♀ for less than 1 hr. No treatment-related effects on mortality, clinical signs of toxicity or body weight at 1,000 mg/kg bw/day.	
56-day oral (dietary) toxicity Dog (Beagle) PMRA# 2849783	Supplemental study due to limited group size. 1598/1650 mg/kg bw/day ♂/♀: ↓ leukocytes and platelets (♂).	
28-day range-finding oral (capsule) toxicity Dog (Beagle) PMRA# 1141716	Supplemental study due to limited group size. ≥1000 mg/kg bw/day: ↓ BUN (♂); 2000 mg/kg bw/day: ↑ incidence of bilateral ptosis, ataxia and salivation (1♂), ↑ WBC, ↓ platelets, ↓ testicular/epididymidal wts, ↑ incidence of suppurative inflammation of kidneys, renal tubular mineralization (♂).	
90-day oral with 28-day recovery (capsule) toxicity Dog (Beagle) PMRA# 1141719	NOAEL = 500 mg/kg bw/day 1000 mg/kg bw/day: ↓ absolute thyroid/parathyroid wts (17 wks) (♂); ↓ WBC (12 and 16 wks), ↑ total protein (5 wks), slightly ↑ absolute liver wts (13 wks), ↑ absolute ovarian wts (17 wks) (♀).	
1-yr oral (dietary) toxicity Dog (Beagle) PMRA# 1155893	NOAEL = 342/1352 mg/kg bw/day ♂/♀ 1506/1352 mg/kg bw/day ♂/♀: ↑ adrenal wts, enlarged adrenal glands and adrenal cortical hypertrophy (♂).	
1-yr oral (capsule) toxicity Dog (Beagle) PMRA# 1163655	NOAEL = 500 mg/kg bw/day 1000 mg/kg bw/day: slightly ↓ lung/trachea, testis/epididymides and thyroid/parathyroid wts (♂); slightly ↓ ovarian wts, slightly ↑ adrenal gland wts (♀).	
90-day dermal toxicity Rat (CD) PMRA# 1159167	NOAEL = 390 mg/kg bw/day ♂/♀ (HDT)	

Study type/ Species/Strain/ PMRA#	Doses/Purity	Study results
18-month oncogenicity (dietary) Mouse (CD-1) PMRA# 1148222, 1166029, 1166030, 1166033 and 1166035	NOAEL = 300 mg/kg bw/day 1000 mg/kg bw/day: ↑ incidence of hepatocellular necrosis (compared to second control group), ↓ bw and bwg (wk 16 onwards) (♂); ↑ incidence of amyloidosis (in heart and ovary) (♀). No evidence of oncogenicity.	
18-month oncogenicity (dietary) Mouse (CD-1) PMRA# 1166303, 1166304 and 1166305	NOAEL = 300/1,000 mg/kg bw/day ♂/♀ No treatment-related effect on survival, clinical signs, clinical chemistry, gross or micrcoscopic pathology. 1000 mg/kg bw/day: ↑ incidence of hair loss and ↑ fc; ↓ bw (♂). No evidence of oncogenicity.	
2-yr chronic toxicity/oncogenicity (dietary) Rat (Sprague-Dawley) PMRA# 1148223, 1165825 and 1165836	NOAEL = 100/300 mg/kg bw/day ♂/♀ 300 mg/kg bw/day: hepatocellular necrosis (♂); 1000 mg/kg bw/day: slightly ↓ survival rates; ↑ incidence of hyperplasia of submandibular lymph nodes (♂); ↓ bw (90–96 wks) and bwg (90–96 wks), ↑ relative liver wt, ↑ incidence of skeletal muscle atrophy (♀). No evidence of oncogenicity.	
2-yr chronic toxicity/oncogenicity (dietary) Rat PMRA# 1167936, 1167937, 1168076 and 1168077	NOAEL = 320 mg/kg bw/day 1000 mg/kg bw/day: slightly ↑ MCH (up to wk 77), ↓ albumin (wk 105), ↓ absolute brain wt (wk 52), ↑ incidence of mineralization of the renal pelvis (♂); slightly ↓ survival, ↓ bw (at several time-points between wks 66-89), ↑ ALP (wk 105), ↑ total volume of urine (wks 50 and 77) (♀). No evidence of oncogenicity.	
Bacterial reverse mutation test *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 PMRA# 1130115	Negative with and without metabolic activation.	
Bacterial reverse mutation test *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 PMRA# 1207338	Negative with and without metabolic activation.	

Study type/ Species/Strain/ PMRA#	Doses/Purity	Study results
Bacterial reverse mutation test *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 *Saccharomyces cerevisiae* D4 PMRA# 1130113	Supplemental study due to only a single trial being conducted. Negative with and without metabolic activation.	
Bacterial reverse mutation test *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 PMRA# 1231781	Negative with and without metabolic activation.	
Mouse lymphoma forward mutation assay Mouse L5178Y cells PMRA# 1130117	Supplemental study due to only a single trial being conducted. Negative with and without metabolic activation.	
Mouse lymphoma forward mutation assay Mouse L5178Y cells PMRA# 1141771	Supplemental study due to only a single trial being conducted. Negative with and without metabolic activation.	
Chromosome aberrations in vitro CHO cells PMRA# 1130120	Negative with and without metabolic activation.	
Chromosome aberrations in vitro CHO cells PMRA# 1207350	Negative with and without metabolic activation.	
Unscheduled DNA synthesis Primary rat hepatocytes PMRA# 1130123	Negative.	
Unscheduled DNA synthesis Primary rat hepatocytes PMRA# 1207359	Negative.	
Unscheduled DNA Repair Synthesis Human epithelioid cells (HeLa S3)	Negative with and without metabolic activation.	

Study type/ Species/Strain/ PMRA#	Doses/Purity	Study results
PMRA# 1231704		
Cell Transformation Assay C3H/10T 1/2 cells, pass 12 PMRA# 1141791	Negative with metabolic activation.	
Cell Transformation Assay C3H/10T 1/2 cells, pass 12 PMRA# 1141790	Negative without metabolic activation.	
Chromosome Aberration Assay - In vivo Rats, Sprague-Dawley, bone marrow cells PMRA# 1141782	Negative.	
2-generation reproductive toxicity (dietary) Rat (CD) PMRA# 1146701	Parental: NOAEL = 1322/1602 mg/kg bw/day ♂/♀ No treatment-related effects. Reproductive: NOAEL = 1322/1602 mg/kg bw/day ♂/♀ No treatment-related effects Offspring: NOAEL = 475 mg/kg bw/day 1,602 mg/kg bw/day: slightly ↓ pup bw (F_1: PNDs 14-21, F_2: PND 21) and bwg (F_1: PNDs 7-14, F_2: PNDs 7-21).	
2-generation reproductive toxicity (gavage) Rat (Sprague-Dawley) PMRA# 1141729 and 1141730	Parental: NOAEL = 1000 mg/kg bw/day No treatment-related effects. Reproductive: NOAEL = 250 mg/kg bw/day ≥500 mg/kg bw/day: ↓ pup birth wt (F_2). Offspring: NOAEL = 250 mg/kg bw/day ≥500 mg/kg bw/day: ↓ pup bw (F_1: PNDs 4-28; F_2: PNDs 1-14) (♂); 1000 mg/kg bw/day: ↓ pup viability (F_2).	
Developmental toxicity (gavage) Rat (Sprague-Dawley)	Maternal: NOAEL = 1,000 mg/kg bw/day No treatment-related effects.	

Study type/ Species/Strain/ PMRA#	Doses/Purity	Study results
PMRA# 1131463, 1166329, 1166330 and 2768309	Developmental: NOAEL = 1000 mg/kg bw/day No treatment-related effects.	
Developmental toxicity (gavage) Rat (Sprague-Dawley) PMRA# 1182863	Supplemental study as only one dosage level was examined. Maternal: No treatment-related effects. Developmental: 1000 mg/kg bw/day: ↑ incidence of extra 14th ribs.	
Range-finding developmental toxicity (gavage) Rat (Sprague-Dawley) PMRA# 1141731	Supplemental study. Maternal: ≥5000 mg/kg bw/day: ↑ incidence of lethargy and ataxia; 7500 mg/kg bw/day: 1 mortality; 10 000 mg/kg bw/day: 2 mortalities. Developmental: No treatment-related effect on the number of implantations or resorptions.	
Developmental toxicity (gavage) Rabbit (New Zealand White) PMRA# 1182862	Supplemental study due to only one dosage level being examined. Maternal: No treatment-related effects. Developmental: 1000 mg/kg bw/day: ↓ fetal wt, ↑ post-implantation loss.	
Developmental toxicity (gavage) Rabbit (New Zealand White) PMRA# 1207326	Maternal: NOAEL = 100 mg/kg bw/day ≥100 mg/kg bw/day: ↓ urination and defecation, small feces (not considered adverse); 1050 mg/kg bw/day: ↑ number of abortions, ↓ bwg (GDs 6-19), ↓ activity, ↓ urination and defecation, small feces. Developmental: NOAEL = 1050 mg/kg bw/day No treatment-related effects. Note: in a range-finding assay, no adverse effects were reported in pregnant animals (6-7/group) receiving 0, 0.4, 4.0, 40, 400 or 1000 mg/kg bw/day.	
Developmental toxicity (gavage) Rabbit (New Zealand White) PMRA# 1141735	Maternal: NOAEL = 500 mg/kg bw/day 1000 mg/kg bw/day: bw loss (GDs 6 to 12), ↓ bwg (GDs 6-19) and fc (GDs 6 to 18), slightly ↓ gravid uterine wt. Developmental: NOAEL = 100 mg/kg bw/day	

Study type/ Species/Strain/ PMRA#	Doses/Purity	Study results
	500 mg/kg bw/day: ↑ percentage of fetuses/litters with 27th presacral vertebrae, ↑ fetal incidence of 13th full ribs; 1000 mg/kg bw/day: ↑ incidence of heart and/or great vessel defects (0, 2, 2 and 3 fetuses in the 100, 500 and 1000 mg/kg bw/day, respectively; the percentage of fetuses (litters) with this finding at this dose level (2.4% (17.6%)) slightly exceeded the maximal incidence in the historical control data (1.9% (14.3%)), slightly ↓ live litter size, ↑ incidence of adactyly and brachydactyly of the #1 digit on both forepaws (4 fetuses/1 litter) (the percentage of fetuses (litters) with adactyly (3.3% (5.9%) was slightly outside the range in the historical control data (0%-0.7% (0%-5.6%). Brachydactyly was not observed in any fetus in the historical control data set. Note: adactyly and brachydactyly considered treatment-related by study author due to occurrence in the range-finding study (not available to the PMRA) 1(1), 7(2) and 8(4) fetuses (litters) at 1000, 2000 and 2500 mg/kg bw/day, respectively. Note: a high number of mortalities was noted in an initial study which was attributed to the presence of pasteurellosis and pneumonia. Since this maternal toxicity hindered the investigation of potential developmental toxicity, this current study was performed. Supplemental findings from the initial study included maternal body weight loss at GDs 6-12 at 1000 mg/kg bw/day, ↑ incidence of 13th full rib in fetuses ≥500 mg/kg bw/day and 27th presacral vertebrae at 1000 mg/kg bw/day.	

Appendix IV Non-occupational and occupational exposure and risk assessment

Table 1 DMH-equivalent rates of DMY and MMY in registered end-use products

Reg. #	Formulation	Amount of a.i. in product (%)	Manufacturing product rate range (ppm) [a]		
			DMY	MMY	DMH-equivalent [b]
25754	Solution	32.3 (DMY); 7.2 (MMY)	1098–4457	245–994	946–3841
25755		45 (DMY); 10 (MMY)	1125–4500	250–1000	969–3875
27295		32 (DMY); 7.5 (MMY)	1088–4416	255–1035	948–3846
25757 [c]	Soluble powder	88.6 (DMY); 5.7 (MMY)	886–8860	57–570	650–6496
25939		93.3 (DMY); 6 (MMY)	933–9330	60–600	684–6841

Reg # = product registration number; a.i. = active ingredient; ppm = parts per million; DMY = 1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin ; MMY = hydroxymethyl-5,5-dimethylhydantoin; DMH = dimethylhydantoin;

[a] Rate range of DMY/MMY on the commercial-class end-use product labels as a material preservative in the manufacturing products used in the formulation of consumer products.

[b] DMY and MMY are the registered active ingredients; however, the rates are expressed as DMH-equivalents, as this compound is formed in the product (as the degradate of DMY and MMY) and is the compound for which the toxicology reference values were determined. DMY and MMY manufacturing product rates were converted to a DMH-equivalent rate based on the following molecular weight conversions: Fraction of DMH that would come from DMY = 0.681; Fraction of DMH the would come from MMY = 0.810. DMH rate (ppm) = (rate DMY (ppm) x 0.681) + (rate of MMY (ppm) × 0.810).

[c] Co-formulated with 3-iodo-2-propynyl n-butylcarbamate (iodocarb).

Table 2 Short- to long-term exposure and risk assessment for residential handlers – DMH

Scenario	Max rate (ppm DMH)[a]	AHPD[b]	Dermal exposure (mg/kg bw/day)[c]	Inhalation exposure (mg/kg bw/day)[d]	Dermal MOE[e]	Inhalation MOE[e]	Combined MOE[f]
					Target MOE = 300		
Airless Sprayer	6841	56.7 L/day	0.5899	0.013	**170**	7700	**170**
	3875[i]		0.3342	0.0074	300	14 000	290
Brush/Roller	6841	7.58 L/day	0.0953	1.39E-5	1000	7 200 000	1000
Aerosol Can		1020 g/day	0.0356	0.0006	2800	170 000	2800
Liquid Pour + Mop		3.79 L/day	0.0329[g]	0.0001[g]	3000	1 700 000	3000
RTU Wipe		0.5 L/day	0.1291	4.52E-5	770	2 200 000	770
Trigger spray bottle + wipe			0.0820	0.0017	1200	57 000	1200
Liquid Pour Into Trigger Spray Bottle + Trigger Spray Bottle + Wipe			0.0873[h]	0.0017[h]	1100	57 000	1100

DMH = dimethylhydantoin; max = maximum; ppm = parts per million; AHPD = amount handled per day; MOE = margin of exposure; DA = dermal absorption; RTU = ready-to-use

Bolded cells indicate where the MOE was less than the target MOE.

[a] Maximum manufacturing rate of DMY and MMY (converted into DMH-equivalent rate) from all registered end-use products. See Appendix IV, Table 1 for more information. This rate is equivalent to 0.00848 kg a.i./L paint if assuming a density of 1.24 g/mL or 0.006841 kg a.i./L cleaning product assuming a density of 1 g/mL ppm of DMH = mg a.i./kg DMH.

[b] USEPA Residential SOP (PMRA# 2409268) standard values for painting and USEPA (2015) standard values for cleaning.

[c] Dermal Exposure (mg/kg bw/day) = (unit exposure × application rate × AHPD × DA (50%))/80 kg. Unit exposures are from AEATF II exposure studies (PMRA# 3003682, 2849401, 2296582, 2169144, 2169213) and the USEPA Residential SOPs (PMRA# 2409268).

[d] Inhalation Exposure (mg/kg bw/day) = (unit exposure × application rate × AHPD/80 kg. Unit exposures are from AEATF II exposure studies (PMRA# 3003682, 2849401, 2296582, 2169144, 2169213) and the USEPA Residential SOPs (PMRA# 2409268).

[e] MOE = NOAEL (mg/kg bw/day)/Exposure (mg/kg bw/day). Based on a NOAEL of 100 mg/kg bw/day from a rabbit oral developmental toxicity study. Target MOE is 300.

[f] Combined MOE = NOAEL (mg/kg bw/day)/(Dermal Exposure (mg/kg bw/day) + Inhalation Exposure (mg/kg bw/day)); Target MOE is 300.

[g] Unit exposures are a sum of the values for the conventional liquid pour scenario and mopping scenario.

[h] Unit exposures are the sum of the values for liquid pour into trigger spray bottle scenario and the trigger spray bottle + wipe scenario.

[i] Maximum manufacturing rate of DMY and MMY from the liquid solution end-use products (converted into DMH-equivalent rates). The concentration of DMY and MMY in these products is lower than the soluble powder end-use products. See Appendix IV, Table 1 for more information. Rate is equivalent to 0.004805 kg/L paint if assuming a density of 1.24 g/mL.

Table 3 Converting rate of DMH-equivalent end-use product rate to free formaldehyde [CH_2O] in solution

DMH (aq) (ppm) [a]	mol DMH/kg solution [b]	mol CH_2O/kg solution [c]	CH_2O (aq) (ppm) [d]	Free CH_2O (ppm) [e]
6841	0.0534	0.1067	3206	32

DMH = dimethylhydantoin; CH_2O = formaldehyde; ppm = parts per million; mol = mole; sol = solution; aq = aqueous (liquid) phase

[a] Maximum rate of DMH in manufacturing products from the end-use product labels (see Appendix IV, Table 1). Used as a part of a Tier 1 assessment as it addresses product rates for all other manufacturing and consumer products.

[b] mol DMH/kg solution = [DMH (ppm = mg/kg sol)]/molar mass DMH (128.17 g/mol) × 0.001 (mg to g conversion)

[c] mol CH_2O/kg solution = mol DMH/kg solution × 2 (2 molecules of CH_2O per 1 molecule of DMH)

[d] ppm total CH_2O in aqueous solution (CH_2O (aq)) = mol CH_2O/kg solution × molar mass CH_2O (30.031 g/mol) × 1000 (g to mg conversion)

[e] 1% of total CH_2O in the aqueous solution is available for potential volatilization (free formaldehyde).

Table 4 Calculation of the formaldehyde [CH_2O] air concentration corresponding to the concentration of free formaldehyde [CH_2O] in solution to an air concentration (ppm)

Concentration of free CH_2O (aq) (ppm) [a]	Concentration of CH_2O (vapour) (ppm) [b]
32	0.004

CH_2O = formaldehyde; aq = aqueous (liquid) phase; ppm = parts per million; T = temperature; vapour = vapour phase (in the air)

[a] Value obtained from Appendix IV, Table 3.

[b] The original equation from PMRA# 3244217 was rearranged to calculate the concentration of formaldehyde in vapour. Original equation = [CH_2O (aq)] = 10 [(453.8/T) – 11.34] × [CH_2O (vapour)] [(252.2/T) + 0.2088]; T = 295.15 Kelvins (corresponds to 22ºC).

Table 5 Short- to long-term inhalation exposure and risk assessment for residential handlers - formaldehyde (CH_2O)

Air concentration of CH_2O in vapour (mg/m^3) [a]	Inhalation exposure (µg/kg bw/day) [b]	Inhalation MOE [c] Target MOE = 100
0.0051	0.0002	560

CH_2O = formaldehyde; MOE = margin of exposure

[a] Calculated air concentration of CH_2O. See Section 3.3.2 for more information. Maximum air concentration (0.004 ppm from Table 4 above) was converted to $\mu g/m^3$ using: mg/m^3 CH2O = (molecular weight CH_2O (30.031 g/mol) × 0.004 ppm CH_2O)/24.45.

[b] Inhalation Exposure (mg/kg bw/day) = Air Concentration (mg/m^3) × Inhalation Rate (1.02 m^3/hr) × Exposure Time (3 hr) / Body weight (80 kg)

[c] MOE = NOAEL (mg/kg bw/day) / Exposure (mg/kg bw/day). Based on a long-term NOAEC of 0.4 mg/m^3 (~ 0.11 mg/kg bw/day) from a 28-month chronic inhalation toxicity study, as this toxicology reference value addresses shorter exposure durations. Target MOE is 100.

Table 6 Inhalation cancer exposure and risk assessment for residential handlers – Formaldehyde

ADD (mg/kg bw/day) [a]	LADD (mg/kg bw/day) [b]	Cancer risk [c]
0.0002	1.30E-5	2E-6

ADD = absorbed daily dose; LADD = lifetime absorbed daily dose

[a] ADD (mg/kg bw/day) = Inhalation Exposure (mg/kg bw/day) (See Appendix IV, Table 3).

[b] LADD (mg/kg bw/day) = ADD (mg/kg bw/day) × Treatment Frequency (30 days/year) × Exposure Duration (63 years) / (365 days/year × Life Expectancy (78 years))

[c] Cancer risk = LADD × q_1* (1.69×10^{-1} (mg/kg bw/day)$^{-1}$)

Table 7 Short- to long-term exposure and risk assessment for occupational primary handlers (manufacturing) – DMH

Scenario	PPE[a]	Max rate (ppm of DMH[b])	AHPD[c]	Dermal exposure[d] (mg/kg bw/day)	Inhalation exposure[e] (mg/kg bw/day)	Dermal MOE[f]	Inhalation MOE[f]	Combined MOE[g]
						Target MOE = 300		
Liquid Pour	Single Layer + CR gloves	3875	7571 L/day (9388 kg/day)	0.4856	0.0023	206	43000	205
Solid Pour	Single Layer + CR gloves	6841		0.2349	0.4621	430	216	143
	Single Layer + CR gloves + FFR[h]			0.2349	0.0924	430	1100	310

PPE = personal protection equipment; DMH = dimethylhydantoin; MOE = margin of exposure; FFR = filtering facepiece respirator (dust mask); CR = chemical-resistant; AHPD = amount handled per day; UE = unit exposure; DA = dermal absorption; BW = body weight; Max = maximum

Shaded cells indicate where MOE was less than the target MOE.

[a] Single Layer = long-sleeved shirt, long pants.

[b] Maximum manufacturing rates of DMY and MMY (converted into DMH-equivalent rate) from both liquid and soluble powder end-use product labels. See Appendix IV, Table 1 for more information. ppm of DMH = mg a.i./kg DMH.

[c] AHPD is based on the standard value for manufacturing paint. Converted to kg/day based on the density of paint (1.24 g/mL).

[d] Dermal Exposure (mg/kg bw/day) = AHPD × Rate (ppm = mg a.i./kg) × mg to kg conversion (1.0E-6) × UE (µg/kg a.i.) × DA (50%) × ug to mg conversion (1.0E-3)/BW (80 kg). Unit exposures are from AEATF II exposure studies (PMRA# 2296582, 2834812).

[e] Inhalation Exposure (mg/kg bw/day) = AHPD × Rate (mg a.i./kg) × mg to kg conversion (1.0E-6) × UE (µg/kg a.i.) × µg to mg conversion (1.0E-3)/BW (80 kg). Unit exposures are from AEATF II exposure studies (PMRA# 2296582, 2834812).

[f] MOE = NOAEL (mg/kg bw/day)/Exposure (mg/kg bw/day). Based on a NOAEL of 100 mg/kg bw/day from a rabbit oral developmental toxicity study. Target MOE is 300.

[g] Combined MOE = NOAEL (mg/kg bw/day)/(Dermal Exposure (mg/kg bw/day) + Inhalation Exposure (mg/kg bw/day)). Target MOE is 300.

[h] Mitigation (addition of FFR) required to reach target MOEs. This PPE is currently on soluble power end-use product labels.

Table 8 Short- to long-term inhalation exposure and risk assessment for occupational primary handlers (manufacturing) – formaldehyde

Air concentration of CH_2O in vapour (mg/m^3)[a]	Inhalation Exposure (mg/kg bw/day)[b]	Inhalation MOE[c] Target MOE = 100
0.0051	0.0005	210

CH_2O = formaldehyde; MOE = margin of exposure

[a] Calculated air concentration of CH_2O. See Section 3.3.2 for more information. Maximum air concentration (0.004 ppm) was converted to mg/m^3 using: mg/m^3 CH_2O = (molecular weight CH_2O (30.031 g/mol) × 0.004 ppm CH_2O)/24.45.

[b] Inhalation Exposure (mg/kg bw/day) = Air Concentration (mg/m^3) × Inhalation Rate (1.02 m^3/hr) × Exposure Time (8 hr) / Body weight (80 kg)

[c] MOE = NOAEL (mg/kg bw/day)/ Exposure (mg/kg bw/day). Based on a long-term NOAEC of 0.4 mg/m^3 (~ 0.11 mg/kg bw/day) from a 28-month chronic inhalation toxicity study, as this toxicology reference value addresses shorter exposure durations. Target MOE is 100.

Table 9 Inhalation cancer exposure and risk assessment for occupational primary handlers (manufacturing) – formaldehyde

ADD (mg/kg bw/day)[a]	LADD (mg/kg bw/day)[b]	Cancer risk[c]
0.0005	1.84E-4	3E-5

ADD = absorbed daily dose; LADD = lifetime absorbed daily dose

[a] ADD (mg/kg bw/day) = Inhalation Exposure (mg/kg bw/day) (see Appendix IV, Table 8).

[b] LADD (mg/kg bw/day) = ADD (mg/kg bw/day) × Treatment Frequency (250 days/year) × Exposure Duration (40 years) / (365 days/year × Life Expectancy (78 years))

[c] Cancer risk = LADD × q_1* (1.69×10^{-1}(mg/kg bw/day)$^{-1}$)

Table 10 Short- to long-term exposure and risk assessment for secondary handlers – DMH

Scenario	PPE	Max Rate (ppm DMH)[a]	AHPD[b]	Dermal Exposure (mg/kg bw/day)[c]	Inhalation Exposure (mg/kg bw/day)[d]	Dermal MOE[e]	Inhalation MOE[e]	Combined MOE[f]
						Target MOE = 300		
Airless Sprayer	Single layer, no gloves	3875 [g]	120 L/day (148.8 kg/day)	0.2376	0.0156	420	6400	400
		6841 [h]		0.4195	0.0276	**238**	3600	**224**
Brush/Roller		6841 [h]	18.75 L/day (23.25 kg/day)	0.1748	3.44E-5	570	2900000	570
Liquid Pour + Mop			7.57 L/day (7.57 kg/day)	0.0237 [i]	0.0006 [i]	4200	170000	4100
RTU Wipe			1 L/day (1 kg/day)	0.2243	9.05E-5	450	1100000	450
RTU Trigger Spray + Wipe				0.0990	3.49E-3	1000	29000	980
Liquid Pour + Trigger Spray Bottle + Wipe				0.1095 [j]	3.49E-3 [j]	910	29000	890

DMH = dimethylhydantoin; PPE = personal protection equipment; RTU = ready-to-use; ppm = parts per million; AHPD = amount handled per day; MOE = margin of exposure; bw = body weight; Max = maximum; Single layer = long-sleeved shirt, long pants.
Bolded cells indicate where MOE was less than the target MOE.

[a] Maximum manufacturing rates of DMY and MMY (converted into DMH-equivalent rates) from all registered end-use product labels. See Appendix IV, Table 1 for more information. ppm of DMH = mg a.i./kg DMH.

[b] AHPD (L/day) converted to kg/day (when required) based on the density of paint (1.24 g/mL) or cleaning products (1 g/mL).

[c] Dermal Exposure (mg/kg bw/day) = AHPD (kg/day) × Rate (mg a.i./kg) × UE (µg/kg a.i.) × DA (50%) × ug to mg conversion (1.0E-3)/BW (80 kg). Unit exposures are from AEATF II exposure studies (PMRA# 3003682, 2849401, 2296582, 2169144, 2169213).

[d] Inhalation Exposure (mg/kg bw/day) = AHPD (kg/day) × Rate (mg a.i./kg) × UE (µg/kg a.i.) × µg to mg conversion (1.0E-3)/BW (80 kg). Unit exposures are from AEATF II exposure studies (PMRA# 3003682, 2849401, 2296582, 2169144, 2169213).

[e] MOE = NOAEL (mg/kg bw/day)/ Exposure (mg/kg bw/day). Based on a NOAEL of 100 mg/kg bw/day from a rabbit oral developmental toxicity study. Target MOE is 300.

[f] Combined MOE = NOAEL (mg/kg bw/day)/(Dermal Exposure (mg/kg bw/day) + Inhalation Exposure (mg/kg bw/day)). Target MOE is 300.

[g] Maximum rate on solution (liquid) end-use product labels (see Appendix IV, Table 1).

[h] Maximum rate on soluble powder end-use product labels (see Appendix IV, Table 1).

[i] Unit exposures from the AEATF II liquid pour and mopping studies were summed for this scenario.

[j] Unit exposures from the AEATF II liquid pour and wipe studies were summed for this scenario to address exposure for pouring solutions into trigger spray bottle.

Appendix V Proposed label amendments for end-use products containing DMY and MMY

Information on approved labels of currently registered products should not be removed unless it contradicts the label statements provided below.

1. Label amendments for DMY/MMY technical grade active ingredients

- On the primary display panel, include the following signal words: "POTENTIAL SKIN SENSITIZER."
- In the PRECAUTIONS section, include the statement: "Potential skin sensitizer."

2. Label amendments for commercial class end-use products containing DMY/MMY

2.1 General label improvements

Liquid (solution) end-use product labels, under PRECAUTIONS:

Replace: "Wear long-sleeved shirt, long pants, and chemical-resistant gloves when handling the concentrate."

With: "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes when handling the concentrated product or treated process fluids and during clean-up and repair. Remove and wash contaminated clothing before re-use."

Soluble powder end-use product labels, under PRECAUTIONS:

Replace:
"If there is potential to generate dust, wear dust filtering respiratory protection"; or
"In addition, dust filtering respirator protection is required during handling if there is a potential for dust generation"

With:
"In addition, wear a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested when handling the concentrated powder."

Replace:
"Workers must wear a long-sleeved shirt, long pants, chemical resistant gloves and goggles or a face shield during mixing, loading, cleanup and repair"; or
"Wear long-sleeve shirt, long pants, and chemical-resistant gloves and eye protection when handling the concentrate"

With: "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes, and protective eyewear (goggles or a face shield) when handling the concentrated powder or treated process fluids and during clean-up and repair. Remove and wash contaminated clothing before re-use."

2.2 All commercial class liquid (Solutions)

"For use with closed loading and transfer systems only (that is, dry coupling)."

A closed transfer system is defined as a procedure for removing a pesticide from its original container, rinsing the emptied container and transferring the pesticide and rinse solution through connecting hoses pipes, and coupling that are sufficiently tight to prevent exposure of any person to the pesticide or rinse solution. Furthermore, the closed transfer system must be equipped with a dry coupling system that is designed to drip less than 2 mL per coupling.

2.3 DIRECTIONS FOR USE

For the manufacturing of paper coatings, the following statement is proposed:

"**DO NOT** use this product in the production of paper coatings that will come in contact with food."

For end-use products Reg. No. 25754, 25755, 25939, and 27295:

Remove the following statement under the Precautions section:

"Do not discharge into lakes, streams, rivers or ponds."

For end-use product Reg. No. 25757:

Remove the following statement under the DIRECTIONS section

"DO NOT discharge effluents containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters."

Add the following statement under the DIRECTIONS FOR USE section for all products:

"This registration is granted under the *Pest Control Products Act* and does not exempt the user from any other legislative requirements.

Use of this product and management of any resulting discharge or release of effluents containing this product must also be in accordance with the *Fisheries Act* and with any other applicable federal or provincial legislation.

Consult with provincial regulatory authorities on any authorizations or other requirements for use of this product and management of any resulting discharge or release of effluents containing this product."

References

A. Information considered in the updated chemistry assessment

List of studies/information submitted by registrant

PMRA Document Number	Title
1795931	DMY/MMY- Product Chemistry for Glycoserve, DACO: 2.1, 2.10, 2.11, 2.12, 2.13, 2.14.1, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.7, 2.14.8, 2.14.9, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9
1796345	1991, DMY/MMY- Product Chemistry for Dantogard XL-1000, DACO: 2.1, 2.11, 2.12, 2.13, 2.14.1, 2.14.14, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8, 2.14.9, 2.16, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9
1796353	1998, DMY/MMY- Product Chemistry for Dantogard XL-1000 Chemistry update. Specifications, Molecular Formula, Octanol/Water Partition Coefficient, Storage Stability data, Risk Assessment of Slimicides,, DACO: 2.99
2762182	2016, Glydant Process, DACO: 2.11.1, 2.11.2, 2.11.3
2762183	2017, Glycoserve (Alternate Name Glydant): Preliminary Analysis, DACO: 2.13.3
2762190	2016, Glydant Process, DACO: 2.11.1, 2.11.2, 2.11.3
2762191	2017, Dantogard XL-1000: Preliminary Analysis, DACO: 2.13.3

B. Information considered in the updated toxicology assessment

List of studies/information submitted by registrant

PMRA Document Number	Title
1123384	Acute oral toxicity in rats - Median lethal dosage determination with Dantogard XL-1000). November 1, 1990.. DACO 4.2.1.
1123385	Acute dermal toxicity in rabbits - limit test with Dantogard XL-1000. November 1, 1990. DACO 4.2.2.
1123388	Primary skin irritation study in rabbits with Dantogard XL-1000. November 1, 1990. DACO 4.2.5.
1123389	Primary eye irritation study in rabbits with and without rinsing with Dantogard XL-1000. November 1, 1990. DACO 4.2.4.
1130094	Rabbit eye irritation study, Compound: Dantoin DMDMH-55. February 10, 1978. DACO 4.2.4.
1130095	Acute Oral LD50, Acute Primary Dermal Irritation, Acute Primary Eye Irritation and Acute Dermal LD50. September 30, 1976. DACOs 4.2.1., 4.2.2, 4.2.3., 4.2.4, 4.2.5.
1130096	Acute Inhalation Toxicity of Glydant in Sprague-Dawley Rats. November 13, 1981. DACO 4.2.3.
1130104	90-Day Oral Toxicity of Glydant in Sprague-Dawley Rats. March 16, 1982. DACO 4.3.1.
1130105	28/91 Day Subchronic Percutaneous Toxicity Study in Rabbits with G0047.02. June 1st, 1983. DACO 4.3.4.
1130108	Mutagenicity Evaluation of Dantoin DMDMH-55 40-697 737543 in the Ames Salmonella/microsome Plate Test. March 7, 1978. DACO 4.5.4.
1130109	Salmonella/Mammalian-Microsome Preincubation Mutagenicity Assay. September 3, 1982. DACO 4.5.4.
1130110	Salmonella/Mammalian-Microsome Mutagenesis Assay. February 19, 1982. DACO 4.5.4.
1130113	Mutagenicity Evaluation of Dimethyl Hydantoin 40-683 635658 in the Ames Salmonella/Microsome Plate Test Final Report. March 7, 1978. DACO 4.5.4.

PMRA Document Number	Title
1130115	Salmonella/ Mammalian-microsome Preincubation Mutagenicity Assay (Ames Test): Dimethylhydantoin. September 3, 1982. DACO 4.5.4.
1130116	Test for chemical induction of mutation in mammalian cells in culture. The L5178Y TK± mouse lymphoma assay. April 29, 1982. DACO 4.5.4.
1130117	L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay. January 11, 1983. DACO 4.5.4.
1130119	Cytogenicity Study - Chinese Hamster Ovary (CHO) Cells in Vitro. May 24, 1982. DACO 4.5.4.
1130120	Cytogenicity Study - Chinese Hamster Ovary (CHO) Cells In Vitro. September 3, 1982. DACO 4.5.4.
1130123	Unscheduled DNA Synthesis in Primary Cultures of Rat Hepatocytes (by Autoradiography). October 29, 1982. DACO 4.5.4.
1131463	Developmental toxicity evaluation of 5,5-dimethylhydantoin (DMH) administered by gavage to CD rats. July 30, 1992. DACO 4.5.2.
1141714	28-Day Dietary Study in Mice with DMH. March 7, 1991. DACO 4.3.1.
1141715	Four Week Range-Finding Oral Gavage Study in Rats with Dimethylhydantoin (DMH). June 14, 1982. DACO 4.3.1.
1141716	28-Day Oral (Capsule) Study in Beagle Dogs with DMH Final Report. November 12, 1991. DACO 4.3.2.
1141717	90-Day Dietary Study in Mice with DMH Final Report. March 7, 1991. DACO 4.3.1.
1141719	13-Week Oral (Capsule) Study in Dogs with DMH Final Report. July 21, 1992. DACO 4.3.2.
1141722	Acute Oral Toxicity (LD50) Study in Albino Mice with DMH. September 6, 1989. DACO 4.2.1.
1141723	Acute Oral Study in Beagle Dogs with DMH Final Report. March 10, 1993. DACO 4.2.1.
1141726	Skin Sensitization Study in Albino Guinea Pigs with Dimethylhydantoin. July 17, 1989. DACO 4.2.6.
1141729 and 1141730	Two-Generation Reproduction Study of Dimethylhydantoin Administered Orally in Rats Final Report. July 24, 1992. DACO 4.5.1
1141731	A Range-finding Teratology Study in Rats with 5,5-Dimethylhydantoin Final Report. December 21, 1982. DACO 4.5.2.
1141735	1992. A developmental toxicity study of Dimethylhydantoin in Rabbits. June 23, 1992. DACO 4.5.3.
1141771	Mouse Lymphoma Forward Mutation Assay Dimethylhydantoin: Final Report. October 29, 1982. DACO 4.5.4.
1141782	In vivo Bone Marrow Cytogenetic Assay in Rats 5,5-Dimethylhydantoin (DMH) Final Report. October 26, 1982. DACO 4.5.4.
1141790	Cell Transformation Assay Dimethylhydantoin Without Metabolic Activation Final Report. January 18, 1983. DACO 4.5.4.
1141791	Cell Transformation Assay Dimethylhydantoin with Metabolic Activation Final Report. January 18, 1983. DACO 4.5.4.
1146701	Two-generation reproduction study in CD rats with 5,5-dimethylhydantoin (DMH) administered in the diet. June 16, 1994. DACO 4.5.1.
1148222, 1166029, 1166030, 1166033 and 1166035	Chronic dietary oncogenicity study with 5,5-dimethylhydantoin (DMH) in CD-1 Mice. August 31, 1994. DACO 4.4.1.
1148223, 1165825 and 1165836	Chronic dietary toxicity/ oncogenicity study with 5,5-dimethylhydantoin (DMH) in rats. August 31, 1994. DACO 4.4.1.
1153695 and 1153696	90-Day Oral Gavage Study in Rats Dosed with Dimethylhydantoin. January 10, 1983. DACO 4.3.1.
1155893	Evaluation of Dimethylhydantoin (DMH) in a One-year Chronic Dietary Toxicity Study in Dogs. January 6, 1995. DACO 4.4.5.

PMRA Document Number	Title
1159167	Ninety-day dermal toxicity study with 5,5-dimethylhydantoin (DMH) in CD rats. March 10, 1994. DACO 4.3.4.
1161407	Acute inhalation toxicity limit test of Dantogard XL-1000, Lot #A3510008 in rats. January 6, 1994. DACO 4.2.3.
1163655	One-Year Oral Toxicity Study in Dogs with DMH Final Report. March 14 1995. DACO 4.4.1.
1166017	Historical Control Data For Fetal Variations and Malformations From Rabbit Teratology Studies. DACO 4.5.3.
1166019	Historical Control Data For Fetal Variations and Malformations From Rat Teratology Studies. DACO 4.5.2.
1166022	Historical Control Pathology Data for Dog Chronic Toxicity Studies. DACO 4.4.5.
1166023	Historical Control Data 90-Day Oral Gavage (CD Rats). DACO 4.3.1.
1166303, 1166304 and 1166305	18-Month Dietary Oncogenicity Study in Mice with DMH Final Report. May 23, 1996. DACO 4.4.1.
1166329 and 1166330	Regrouping and Tabulation of Skeletal Variations in the Study Entitled "Developmental Toxicity Evaluation of 5,5-Dimethylhydantoin (DMH) Administered by Gavage to CD Rats". Fetal and Litter Incidence Data for Select Skeletal Variations: Skull plates and face, fore and hindlimbs, Centra. July 8, 1996. DACO 4.5.2.
1167936, 1167937, 1168076 and 1168077	Combined 24-month Toxicity/Oncogenicity Study in Rats with DMH Final Report. July 30, 1996. DACO 4.4.1.
1171147	Distribution Study of 1,3-Dihydroxymethyl-5,5'-Dimethylhydantoin-5-14C on Male Sprague-Dawley Rats. August 29, 1983. DACO 4.5.9.
1171148	Distribution study of 5,5'-Dimethylhydantoin-5-14C (C5H8N2O2) in New Zealand White Rabbits. July 30, 1986. DACO 4.5.9.
1182862	Developmental Toxicity Study in Rabbits on Ethyl-Methyl-Hydantoin and Dimethyl-Hydantoin Limit Test. August 6, 1986. DACO 4.5.3.
1182863	Developmental Toxicity Study in Rats on Ethyl-Methyl-Hydantoin and Dimethyl-Hydantoin Limit Test. August 12, 1986. DACO 4.5.2.
1196985	Acute Oral Toxicity in Rats - Median Lethal Dosage Determination with Dantogard II. November 22, 1991. DACO 4.2.1.
1196986	Acute Dermal Toxicity Study with Dantogard II in Rabbits. April 6, 1998. DACO 4.2.2.
1196989	Primary Eye Irritation Study in Rabbits with Dantogard II. November 7, 1991. DACO 4.2.4.
1196990	Primary Skin Irritation Study in Rabbits of: Dantogard II. November 7, 1991. DACO 4.2.5.
1197006	Acute Oral Toxicity in Rats - Median Lethal Dosage Determination of Glycoserve II. December 12, 1991. DACO 4.2.1.
1197007	Acute Dermal Toxicity Limit Test with Glycoserve II. August 31, 1998. DACO 4.2.2.
1197008	Acute Dermal Toxicity in Rabbits - Limit Test with Glycoserve II. November 11, 1991. DACO 4.2.2.
1197009	Acute Inhalation Toxicity Test with Glycoserve II. August 31, 1998. DACO 4.2.3.
1197010	Primary Eye Irritation Test with Glycoserve II. August 31, 1998. DACO 4.2.4.
1197011	Primary Eye Irritation Study in Rabbits with Glycoserve II. November 11, 1991. DACO 4.2.4.
1197012	Primary Skin Irritation Test with Glycoserve II. August 31, 1998. DACO 4.2.5.
1197013	Primary Skin Irritation Study in Rabbits with Glycoserve II. November 11, 1991. DACO 4.2.5.
1197014	Dermal Sensitization Test - Buehler Method with Glycoserve II. August 31, 1998. DACO 4.2.6.
1207326	Rabbit Teratogenicity Study 5,5-Dimethylhydantoin. July 30, 1986. DACO 4.5.3.
1207338	Salmonella/Mammalian Microsome Plate Incorporation Mutagenicity Assay (Ames Test). April 1, 1986. DACO 4.5.4.
1207350	Chromosome Aberration Assay in Chinese Hamster Ovary (CHO) Cells Test Article 5,5-dimethylhydantoin. May1, 1986. DACO 4.5.4.

PMRA Document Number	Title
1207359	Unscheduled DNA Synthesis in Rat Primary Hepatocytes Test Article 5,5-dimethylhydantoin. May 5, 1986. DACO 4.5.4.
1229251	Primary Dermal Irritation Study on 5-Ethyl-5-Methylhydantoin. April 17, 1986. DACO 4.2.5.
1229252	Primary Dermal Irritation Study on 5,5-Dimethylhydantoin. April 17, 1986. DACO 4.2.5.
1229253	Primary Eye Irritation Study on 5-Ethyl-5-Methylhydantoin (EMH). April 18, 1986. DACO 4.2.4.
1229256	Delayed Contact Hypersensitivity Study in Guinea Pigs with 5,5-Dimethylhydantoin (DMH). October 27, 1986. DACO 4.2.6.
1231704	Assessment of Unscheduled DNA Repair Synthesis in Mammalian Cells After Exposure to 5,5-Dimethylhydantoin (DMH). May 19, 1986. DACO 4.5.4.
1231780	Dimethylhydantoin Subchronic Toxicity in Rats: Administration in Drinking Water. December 3, 1986. DACO 4.3.1.
1231781	Dimethyl Hydantoin Assessment of Mutagenic Potential in Histidine Auxotrophs of Salmonella Typhimurium (The Ames Test). February 24, 1986. DACO 4.5.4.
1239416	90-Day Subchronic Oral Toxicity Study in Rats with Dimethylhydantoin Final Report. July 25, 1991. DACO 4.3.1.
1246604	Acute Oral Toxicity Study Ethylmethylhydantoin. December 29, 1982. DACO 4.2.1.
1246605	Salmonella/Mammalian-microsome preincubation Mutagenicity Assay (Ames Test) 5-ethyl-5-methylhydantoin. September 3, 1982. DACO 4.5.4.
1246606	Cytogenicity Study - Chinese Hamster Ovary (CHO) Cells In Vitro 5-ethyl-5-methylhydantoin. October 1, 1982. DACO 4.5.4.
1246607	Unscheduled DNA Synthesis in Primary Cultures of Rat Hepatocytes (By Autoradiography) 5-ethyl-5-methylhydantoin. October 29, 1982. DACO 4.5.8.
1246608	L5178Y +/- Mouse Lymphoma Mutagenesis Assay 5-Ethyl-5-Methylhydantoin. December 29, 1982. DACO 4.5.4.
1841514	Acute Oral Toxicity Study Ethylmethylhydantoin. December 29, 1982. DACO 4.2.1.
1841517	Primary Eye Irritation Study on 5,5-Dimethylhydantoin (DMH). April 18, 1986. DACO 4.2.4.
1841519	Delayed Contact Hypersensitivity Study in Guinea Pigs with 5-Ethyl-5-Methylhydantoin (EMH). October 27, 1986. DACO 4.2.6.
2768303	Absorption, Distribution, Metabolism and Excretion (ADME) Studies of 5-ethyl, 5-methylhydantoin in the rat. November 15, 1991. DACO 4.5.9.
2768304	Addendum to Report Entitled “Absorption, Distribtuion, Metaoblism and Excretion (ADME) Studies of 5 ethyl, 5-methylhydantoin in the Rat”. November 15, 1991. DACO 4.5.9.
2768305	Absorption, Distribution, Metabolism and Excretion (ADME) Studies of 5,5-dimethylhydantoin in the Rat. November 15, 1991. DACO 4.5.9.
2768306	Addendum to Report Entitled “Absorption, Distribution, Metabolism and Excretion (ADME) Studies of 5,5-dimethylhydantoin in the Rat”. November 15, 1991. DACO 4.5.9.
2768307	Developmental Toxicity Study in Rabbits with 5-Ethyl-5-Methylhydantoin (EMH). February 3, 1992. DACO 4.5.3.
2768309	Report Amendment. Developmental toxicity evaluation of 5,5-dimethylhydantoin (DMH) administered by gavage to CD rats. May 31, 1995. DACO 4.5.2.
2849783	United States Environmental Protection Agency Data Evaluation Record. Evaluation of dimethylhydantoin in an eight-week dietary toxicity study in dogs. February 14, 1996. DACO 4.3.2.

Additional information considered

i) Published information

PMRA Document Number	Title
2831829	California Environmental Protection Agency, Department of Pesticide Regulation, Medical Toxicology Branch, Summary of Toxicology Data 1,3-dichloro-5,5-dimethylhydrantoin [5,5-dimethylhydantoin or DMH], October 19th, 2001. DACO 12.5.4.
2831831	United States Environmental Protection Agency, Prevention, Pesticides and Toxic Substances (7510P), 2,4 Imidazolidinedione (Hydroxymethyldimethyl Hydantoins) Summary Document Registration Review, June 2007. DACO 12.5.4.
2831838	United States Environmental Protection Agency, Prevention, Pesticides and Toxic Substances (7510P), Reregistration Eligibility Decision for Halohydantoins (Case 3055), September 2007. DACO 12.5.4.
2849758	Final report on the Safety Assessment of DMDM Hydantoin. Journal of the American College of Toxicology, 1988, 7(3): 245-278. DACO 4.8.
2849774	Contact allergy from DMDM hydantoin, 1994-2000. Contact Dermatitis, 2002, 47(1): 57-8. DACO 4.8.
2849775	Patch Testing with Preservatives, antimicrobials and Industrial Biocides. Results from a Multicentre Study. British Journal of Dermatology, 1998, 138: 467-746. DACO 4.8.
2849776	Patch test reactivity to DMDM hydantoin. Relationship to formaldehyde allergy. Contact Dermatitis, 1988, 18(4): 197-201. DACO 4.8.
2849777	Temporal trends of preservative allergy in Denmark (1985-2008). Contact Dermatitis, 2010, 62: 102-108. DACO 4.8.
2849779	North American contact dermatitis group patch test results: 2011-2012. Dermatitis, 2015, 26(1): 49-59. DACO 4.8.
2849780	Patch testing with formaldehyde and formaldehyde-releasers: multicentre study in Spain (2005-2009). Contact Dermatitis, 2011, 65(5): 286-92. DACO 4.8.
2849781	Sensitivity of petrolatum and aqueous vehicles for detecting allergy to imidazolidinylurea, diazolidinylurea and DMDM hydantoin: a retrospective analysis from the North American Contact Dermatitis Group. Dermatitis, 2007, 18(3): 155-62. DACO 4.8.
2973553	Environment Canada and Health Canada, Canadian Environmental Protection Act, 1999, Priority Substances List Assessment Report Formaldehyde. February 2001. DACO 12.5.4.
2973569	United States Environmental Protection Agency, National Center for Environmental Assessment, Integrated Risk Information System (IRIS) Chemical Assessment Summary, Formaldehyde. October 1st, 1990. DACO 12.5.4.
2977582	Results of a 28-month chronic inhalation toxicity study of formaldehyde in male Fischer-344 rats. Journal of Toxicological Sciences, 1997, 22(3): 239-254. DACO 4.8.
2977583	Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Research, 1983, 43(9): 4382-4392. DACO 4.8.
2977584	Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells. Cancer Research, 1996, 56(5): 1012-1022. DACO 4.8.
2977585	Two-year drinking water study of formaldehyde in rats. Food and Chemical Toxicology, 1989, 27(2): 77-87. DACO 4.8.

C. Information considered in the updated occupational and non-occupational exposure assessment

List of studies/information provided by registrant

PMRA Document Number	Title
1130130	Distribution Study of 5,5'-dimethylhydantoin-5-14C (C5H8N2O2) on Male Sprague-Dawley Rats. 1983. DACO: 6.4.
1130128	Distribution Study of 1,3-Dihydroxymethyl-5,5'-Dimethylhydantoin-5-14C (C7H12N2O4) on Male Sprague-Dawley Rats. 1983. DACO: 6.4.

List of studies/information provided by AEATF II task force

PMRA Document Number	Title
2169144	2010, A Study for Measurement of Potential Dermal and Inhalation Exposure during Application of a Liquid Antimicrobial Pesticide Product Using Bucket and Mop Equipment for Cleaning Indoor Surfaces. DACO: 5.4.
2169213	2011, A Study for Measurement of Potential Dermal and Inhalation Exposure during Application of a Liquid Antimicrobial Pesticide Product Using Trigger Spray and Wipe or Ready-to-Use Wipes for Cleaning Indoor Surfaces. DACO: 5.4.
2296582, 2296584	2012, A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of a Liquid Containing an Antimicrobial, DACO: 5.4.
2834812	2016, A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of Two Solid Formulations Containing an Antimicrobial. DACO: 5.4.
3003682	2019, A Study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial using an Airless Sprayer. DACO: 5.4.
2992785	2017, A study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing and Antimicrobial using an Airless Sprayer. DACO: 0.7.1.
2849401	2018, A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of a Latex Paint Containing an Antimicrobial Pesticide Product Using a Brush and Roller for Indoor Surface Painting. DACO: 5.4.

Additional information considered

Published information

PMRA Document Number	Title
3244217	Dong, S. and P.K. Dasgupta. 1986. Solubility of Gaseous Formaldehyde in Liquid Water and Generation of Trace Standard Gaseous Formaldehyde. Journal of Environmental Science and Technology. 20 (6): 637 – 640.
3244211	USEPA, 2007. Reregistration Eligibility Decision for Halohydantoins (Case 3055). United States Environmental Protection Agency. September 2007.
2409268	USEPA, 2012. Standard Operating Procedures for Residential Pesticide Exposure Assessment. EPA: Washington, DC. Revised October 2012. Section 10.

Unpublished information

PMRA Document Number	Title
1141736	1989, Dermal Absorption of 14-C-Dimethylhydantoin in Rats. Final Report. DACO: 6.4.
3120537	USEPA, 2015. Antimicrobial Division's (AD) Standard Operating Procedures (SOPs) for Residential Exposure Assessments. Working Draft. May 12, 2015.
3084493	USEPA, 2018. Summary of Amounts Handled or Treated for Occupational Handler Scenario. Draft. November 28, 2018.
2877043	2008, UK Exposure Study, DACO: 5.10.

D. Information Considered in the Updated Environmental Assessment

List of studies/information submitted by the registrants

PMRA Document Number	Title
2768313	Hydrolysis of Dimethylhydantoin as a function of pH at 25C. DACO8.2.3.2
2768314	Determination of the Aqueous Photolysis Rate of Dimethylhydantoin. DACO8.2.3.3.2

Additional information considered

Published information

PMRA Document Number	Title
2973553	Canada, 2001. Canada Environmental Protection Act, 1999. Priority Substances List Assessment Report: Formaldehyde. Environment Canada. Health Canada. February 2001
3244211	USEPA 2007. Reregistration Eligibility for Halohydantoins. United States Environmental Protection Agency. September 2007
2996270	USEPA, 2008. Reregistration Eligibility Decision for Formaldehyde and Paraformaldehyde. United States Environmental Protection Agency. June 2008