Proposed Special Review Decision PSRD2020-01

Special Review of Diodofon and Its Associated End-use Products

Consultation Document

(publié aussi en français)

9 July 2020

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

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
hc.pmra.publications-arla.sc@canada.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
hc.pmra.info-arla.sc@canada.ca

Canada

ISSN: 2561-6366 (online)

Catalogue number: H113-30/2020-1E (print)
H113-30/2020-1E-PDF (PDF version)

Table of Contents

1.0 Introduction

Pursuant to subsection 17(1) of the *Pest Control Products Act*, Health Canada's Pest Management Regulatory Agency (PMRA) initiated a special review of diodofon (Canada, 2016) based on the toxicology and exposure information submitted under section 12 of the *Pest Control Products Act*, following the re-evaluation of diodofon (Canada, 2010a; Canada, 2010b).

Pursuant to subsection 18(4) of the *Pest Control Products Act*, Health Canada has evaluated the aspects of concern that prompted the special review of pest control products containing diodofon. The aspects of concern for this special review are relevant to human health.

2.0 Uses of Diodofon in Canada

Diodofon is an antimicrobial active ingredient used as a material preservative in a variety of aqueous based products and building materials (for example, pigment dispersions, caulks and adhesives (ceramic tile adhesives, vinyl wallpaper pastes), wallboard joint compound, mastics, and latex exterior and interior paints) to provide protection against bacterial and fungal degradation of the finalized products. It is also used in leather tanning to protect tanned leather from mould and mildew during in-tanning wet processing and during storage and transportation. All currently registered pest control products containing diodofon (Appendix I) are considered in this special review.

3.0 Aspects of Concern that Prompted the Special Review

Health Canada reviewed toxicology and occupational/residential exposure information submitted under Section 12 of the *Pest Control Products Act* (Appendix II) and re-examined the existing toxicology database for diodofon, in accordance with PMRA practices. This resulted in new diodofon toxicology reference values for occupational and residential risk assessments (Appendix III, Table 2). Consequently, the following aspects of concerns were identified for the special review under subsection 17(1) of the *Pest Control Products Act*:

- Potential applicator risks (workers mixing/loading/applying)
- Potential postapplication risks (occupational and residential)

4.0 Evaluation of the Aspects of Concern that Prompted the Special Review

Following the initiation of the special review of diodofon, Health Canada requested information from provinces and other relevant federal departments and agencies, in accordance with subsection 18(2) of the *Pest Control Products Act*. No information was received relating to the aspects of concern.

In order to evaluate the aspects of concern for diodofon, Health Canada has considered currently available relevant scientific information, which includes information submitted under section 12 of the *Pest Control Products Act* following the re-evaluation of diodofon (Appendix II), information considered during the re-evaluation (Canada, 2010a; Canada, 2010b) and information submitted by the Antimicrobial Exposure Assessment Task Force II (AEATF II).

The evaluation of the aspects of concern of diodofon under this special review is aligned with the approach for assessing pesticides used as preservatives in paints, coatings and related uses (Re-evaluation Note REV2018-02, *Approach for the Re-Evaluation of Pesticides Used as Preservatives in Paints, Coatings and Related Uses*).

Occupational and residential risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies (Appendix III, Table 2) 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.

4.1 Hazard Assessment

4.1.1 Toxicology Summary

Based on the information submitted under section 12 of the *Pest Control Products Act* (Appendix III, Table 1), Health Canada updated the toxicology reference values for diodofon (Appendix III, Table 2).

In laboratory animals, diodofon was of low acute toxicity via the oral and dermal route of exposure and of slight acute toxicity via the inhalation route. It was severely irritating to the eyes and minimally irritating to the skin. Diodofon was not a dermal sensitizer.

The thyroid gland is a target organ of toxicity following repeated oral dosing. No chronic toxicity or carcinogenicity studies were available. Diodofon was not genotoxic. With the exception of skeletal variations in one rabbit developmental toxicity study, developmental toxicity (including increased incidences of malformations and fetal loss) occurred in the presence of maternal toxicity. In reproductive toxicity studies, effects on pup survival at birth and during the lactation period were also noted at maternally toxic levels.

In the 28-day rat dermal toxicity study, very slight changes in thyroid gland pathology occurred at all dose levels in males and in mid- and high-dose females. In addition, there was an increase in thyroid weight in animals receiving the highest dose level. Dermal irritation, accompanied by histologic changes at the dermal test site, was noted at the mid-dose level and above in females and at the high-dose level in males.

In the 90-day rat inhalation toxicity study, degenerative effects and histologic changes were observed in the nasal and respiratory tissues of mid- and high-dose animals. Inhalation exposure to diodofon also resulted in increased lung weight in high-dose males. Treatment-related mortalities, with lung or tracheal lesions that contributed to death, were reported in animals of the high-dose group. Additionally, mortality was reported in one mid-dose male rat but the cause was unclear. Cysts with keratinous debris were found in the thyroid gland of animals across all groups, including controls, with the incidence in high-dose females considered toxicologically significant. Histologic changes in the form of altered tinctorial properties were also observed in the thyroid gland of mid- and high-dose animals. It was unknown if autolysis of the thyroid gland noted in three high-dose males masked any thyroid effects of consequence.

4.1.2 *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 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.

Regarding the completeness of the diodofon toxicity database, the standard complement of prenatal and postnatal studies was available. Available studies included a gavage developmental toxicity study in the rat and two gavage developmental toxicity studies in the rabbit, as well as a published dietary rat developmental toxicity study. A one-generation and a two-generation reproductive toxicity study conducted in rats via the dietary route were also available.

In the gavage rat developmental toxicity study, decreased litter sizes and fetal body weights, as well as increases in resorptions, umbilical hernia, and incomplete ossification were observed. However, concern for these findings was tempered by the fact that they were observed in the presence of maternal toxicity (decreased food consumption and body weight gain). Serious toxic effects were also observed in a rabbit developmental toxicity study, but at lower dose levels compared to the rat study. These effects included decreases in litter size and postnatal survival, as well as increases in the incidence of resorptions and hydrocephalus. The concern for these serious developmental findings in the rabbit was tempered by the fact that they were observed in the presence of maternal toxicity, which included clinical signs and reduced body weight gain, as well as mortality at the highest dose level. Reduced fetal body weight was also observed in the presence of maternal toxicity. In the same rabbit study, there was evidence of sensitivity of the young in view of the finding of an increase in fetal and litter incidence of skeletal variations occurring in the absence of maternal toxicity. The other two developmental toxicity studies in the database did not show evidence of developmental toxicity.

In the one-generation rat reproductive toxicity study, parental animals had decreased body weights, body weight gain, and food consumption, as well as red perinasal soiling down to the lowest dose level tested. Additional findings in high-dose parental animals included mortality, as well as effects in the thyroid gland, including histologic changes, decreased serum triiodothyronine (T3) levels, and increased thyroid-stimulating hormone (TSH) levels. Reproductive toxicity at the mid- and high-dose levels was evident in the form of decreases in gestation survival, live born pups, litter size, and postnatal day (PND) 1 body weight, as well as an increased incidence of stillborn pups. Toxicity in the mid-dose level offspring was noted as decreases in pup survival, body weight, body weight gain, and pup activity, as well as an increased number of dead pups, pups with pale skin, cannibalized pups, pups cold to the touch, and whole litter loss. At the highest dose level, all offspring were terminated by the second post-natal day due to excessive neonatal mortality.

In the two-generation rat reproductive toxicity study conducted with lower dose levels than the one-generation study, increased organ weight and histologic changes were noted in the thyroid gland of parental animals at all dose levels. Parental rats also showed decreased food consumption and body weights at the mid- and high-dose levels. High-dose parental animals had histologic changes in the pituitary gland, and there were two mortalities due to dystocia.

Reproductive toxicity was noted at the high-dose level as increased post-implantation loss and decreased litter size and live birth index. Decreases in the pup survival index and pup weight were noted in offspring from the high-dose level; marginal effects were seen in the mid-dose level offspring.

In summary, the complement of toxicity studies relating to prenatal and postnatal toxicity was adequate to assess potential sensitivity of the young. Sensitivity of the young was evident only in the rabbit developmental toxicity study in the form of an increased incidence of skeletal variations occurring in the absence of maternal toxicity; however, the increase was relatively minor and the endpoints selected for risk assessment are considered protective of this effect. Serious effects (resorptions, malformations, and reduced postnatal survival) occurred at higher dose levels and only in the presence of maternal toxicity, thus lessening the level of concern. These serious effects would warrant a *Pest Control Products Act* factor (PCPA factor) of 3-fold if used for the point of departure for risk assessment, otherwise the PCPA factor would be reduced to 1-fold.

4.2 Residential and Occupational Toxicology Reference Values

For residential and occupational dermal risk assessments, the endpoint was selected from a 28-day dermal toxicity study in the rat. At the lowest observed adverse effect level (LOAEL) of 20 mg/kg bw/day (lowest dose level tested) in males, minor histologic changes were noted in the thyroid gland consisting of very slight follicular cell hypertrophy and altered tinctorial properties. The target MOE for short- and intermediate-term exposure durations was 100, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The target MOE for long-term exposure durations was 1000, which included standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as an additional 10-fold uncertainty factor for extrapolation to a long-term scenario, as the available oral data suggested increased toxicity was associated with increased duration of dosing. No additional uncertainty factor for use of a LOAEL was applied since the level of response at this dose level was considered to be close to the threshold. For residential scenarios, the PCPA factor was reduced to 1-fold as discussed under the *Pest Control Products Act* Hazard Characterization Section. The selection of this study and target MOEs provides a margin of ≥200 (when considering a dermal absorption estimate of 10% from a dermal toxicokinetic study in rats) to the developmental LOAEL for skeletal variations noted previously, and is therefore considered to be protective of all populations, including infants and the unborn children of exposed women.

For occupational and residential inhalation risk assessments, an endpoint from the 90-day inhalation toxicity study in the rat was chosen. Histologic effects in the thyroid gland, and nasal and respiratory tissues were noted at a LOAEL of 13 mg/kg bw/day (LOAEC of 0.007 mg/L). The no observed adverse effect level (NOAEL) was 0.26 mg/kg bw/day (NOAEC of 0.001 mg/L). For the short- and intermediate-term inhalation risk assessments, the target MOE was 100, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For long-term inhalation risk assessments, an additional 3-fold uncertainty factor was applied for extrapolating from an intermediate-term study to a long-term scenario, resulting in a target MOE of 300.

For residential scenarios, the PCPA factor was reduced to 1-fold as discussed under the *Pest Control Products Act* Hazard Characterization Section. The selection of this study and target MOEs is considered to be protective of all adults and children, including infants and the unborn children of exposed women.

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation). For diodofon, exposure via the diet or drinking water is not expected. The toxicological endpoint selected for aggregation was thyroid toxicity. The toxicological reference values and target MOEs established for the relevant route and duration of exposure for the non-aggregate risk assessments are appropriate for use in the aggregate exposure assessment.

Dermal Absorption

As the dermal toxicological reference values are based on a dermal toxicity study, the dermal absorption value is not required.

5.0 Residential and Occupational Exposure and Risk Assessment

5.1 Residential Exposure and Risk Assessment

Residential risk assessment involves estimating risks to the general population, including youth and children, during or after pesticide application.

A residential applicator assessment for the diodofon preservative itself was not required since there are no registered domestic-class pesticide products for paint-related material preservatives. Residential handling of paint-related material preserved with diodofon is considered a postapplication scenario.

The following postapplication scenarios were assessed:

- Individuals applying interior and exterior paints preserved with diodofon;
- Individuals applying building materials (caulks and adhesives (ceramic tile adhesives, vinyl wallpaper pastes), wallboard joint compound and mastics); and
- Individuals who contact surfaces treated with paints and surfaces to which building materials preserved with diodofon have been applied.

5.1.1 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 handling a product that has been treated with a pesticide, or being in a residential environment that has been previously treated with a pesticide.

There is potential for short-term exposure for residential handlers (≥16 years old) applying products preserved with diodofon. The following scenarios were assessed:

- Applying paints with paint brush and roller;
- Applying paints with an airless sprayer;
- Applying building materials; and
- Dermal contact with painted surfaces and surfaces to which building materials were applied.

Paint (Exterior and Interior) Uses

Chemical-specific exposure data were not available for diodofon for the painting scenarios. However, a brush and roller study (PMRA# 2849401) and an airless sprayer study (PMRA# 3003682) were submitted by the Antimicrobial Exposure Assessment Task Force II (AEATF II).

The brush and roller study was designed to quantify dermal and inhalation exposures to both occupational and residential painters while applying paint, containing an antimicrobial, using a brush or roller. The study monitored 18 test subjects using a brush and/or roller in six identical rooms in a warehouse space. The surrogate non-volatile active ingredient used in this study was 1,2-benzisothiazolin-3-one (BIT). The total amount of paint handled (8.520 to 9.940 kg), the time spent while painting (48 to 172 min), and the surface area painted (25 to 82.5 m^2), were all measured. Dermal exposures were measured using inner and outer cotton whole body dosimeters, painter's hat, hand washes (all subjects did not wear gloves) and face and neck wipes. Inhalation exposures were measured using air sampling tubes. Separate dermal unit exposure values were generated for residential painters wearing a short-sleeved shirt and shorts and for occupational workers wearing a long-sleeved shirt, long pants and no gloves. The inhalation unit exposure values for both occupational and residential handlers were generated for each individual performing light activities. The total dermal and inhalation unit exposure values were presented as geometric means based on the arithmetic mean (AMu) of all test subjects.

The airless sprayer study was designed to quantify exposure to painters using airless sprayers. The study monitored 18 test subjects divided into 3 groups based on volume of paint sprayed (37.9 L, 56.8 L and 114 L). The surrogate active ingredient used in this study was propiconazole (PON). Within each group, subjects were subdivided into groups based on dose concentration (0.12% PON or 1.2% PON). All test subjects were occupational painters who had experience painting and handling airless sprayer equipment. The study was conducted in a warehouse facility constructed into three separate modules representing two residential spaces and one commercial office space. All subjects were required to open paint buckets, strain and pour the paint into the equipment and apply paint to the walls, ceiling and other surfaces of the modules. Test subjects wore a long-sleeved shirt and long pants over a 100% cotton dosimeter, as well as a half-face respirator, goggles, shoes and a painter's hat over a dosimeter placed on their head. The test subjects did not wear gloves. Dermal deposition was corrected to account for skin protected by a half-face respirator and goggles. Separate dermal unit exposure values were generated for residential painters wearing a short-sleeved shirt and shorts and for occupational workers wearing a long-sleeved shirt, long pants and no gloves. The inhalation unit exposure values for both occupational and residential handlers were generated for each individual performing light

activities. The total dermal and inhalation unit exposure values were presented as the AMu of all test subjects. There were a number of limitations with the study however, these did not preclude the use of this study to establish unit exposure values for painting with airless sprayers.

The unit exposure values from the brush and roller, and airless sprayer studies, were combined with the default amounts of paint handled per day from the USEPA 2012 Residential SOP (PMRA# 2409268), where a residential painter may apply up to two 1-gallon cans (7.58 L total) daily when using a brush and roller and approximately three 5-gallon cans (56.7 L total) when using an airless sprayer.

The risk assessments for residential handlers applying paint are summarized in Appendix IV, Table 1. Using the unit exposure values from these two studies, assuming the clothing scenario of a residential handler to be shorts and a short-sleeved shirt, together with the default amounts handled, calculated MOEs for residential handlers applying interior paint met the target MOE. Calculated MOEs did not meet the target MOE for dermal and inhalation routes of exposure when applying exterior paint using an airless sprayer; therefore, risks were not shown to be acceptable. To mitigate this risk, it is proposed that the use of diodofon as a preservative in exterior paints be cancelled.

Pigment dispersions containing diodofon are likely to represent only a small component of the overall paint formulation. Therefore, residential exposure to total diodofon residues in paint are not likely to represent a greater exposure than that determined for the paint use only.

To determine the potential transfer of preservative residues from a painted surface, transferable residue studies (PMRA#s 2967976 and 2883917) were submitted by the AEATF II. The studies demonstrated that the transfer of residues onto the skin following contact with a painted surface is minimal. Hence exposure to diodofon is expected to be negligible. Based on the findings of these studies, a quantitative residential postapplication risk assessment for contact with a treated surface for diodofon used in paint was not required and the potential residential postapplication risk is considered to be acceptable.

Building Materials

In the case of building materials, no use description information was provided. Therefore, the default amount of paint handled per day by a residential painter (7.58 L), was used as a surrogate for the amount of building materials handled. Likewise, in the absence of a scenario-specific exposure study, the total body unit exposure values from the brush and roller study were used as a surrogate for applying building materials (except caulks and mastics). For caulks and mastics, where the majority of the exposure is limited to the hands, in comparison to the exposure from applying other building materials (adhesives), only the unit exposure values for the hands from the brush and roller study were considered in the risk assessment.

The risk assessment for individuals applying treated building materials is summarized in Appendix IV, Table 2. Using the appropriate unit exposure values from the brush and roller study, assuming the clothing scenario to be shorts and a short-sleeved shirt, together with the default amounts handled, calculated MOEs for residential handlers applying all building materials met the target MOE and were therefore shown to be acceptable.

The likelihood of diodofon to leach out of dried caulks and adhesives (ceramic tile adhesives, vinyl wallpaper pastes), wallboard joint compound, and mastics is expected to be very limited. This is further supported by the paint transferable residue studies, which demonstrated that the transfer of residues onto the skin following contact with a painted surface is minimal. Therefore transfer of, and dermal postapplication exposure to, diodofon residues is expected to be minimal and not of concern.

Leather

Insufficient data is available to quantitatively assess the residential post-application dermal exposure incurred from contacting or wearing treated leather. This use was not assessed as there was insufficient data to assess exposure from postapplication activities involving leather tanning. Therefore, the use of diodofon in leather tanning operations is proposed for cancellation (see Section 5.2.2.).

Bystander Exposure

Bystander exposure is expected to be negligible for the preservative uses of diodofon.

5.2 Occupational Exposure and Risk Assessment

There is potential for exposure to diodofon in occupational scenarios when workers handle the pesticide during the mixing and loading process in industrial (manufacturing) settings, and for postapplication exposure to workers handling products treated with diodofon.

5.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment

For the commercial-class products used as dry-film preservatives in latex paints (interior and exterior), pigment dispersions, and building materials (latex caulks, mastics and adhesives, wallboard pastes and joint compound), there is potential for exposure to workers who add diodofon during the manufacturing process. For leather tanning, there is the potential for diodofon exposure to workers during mixing and handling of the tanning solution.

Exposure to diodofon from its use in manufacturing facilities is expected to be over an intermediate to long-term duration (that is, >30 days to several months), predominantly via the dermal and inhalation routes.

The commercial class products registered for use in the manufacturing of paints and building materials is formulated as liquids (suspensions) and solids (wettable powder and dust). Therefore, the following scenarios were assessed:

- Mixing/transfer of liquids, open pour;
- Mixing/transfer of solids, open pour.

Chemical-specific exposure data were not available for diodofon for these scenarios. However, the liquid pour (PMRA#s 2296582 and 2296584) and solid pour (PMRA# 2834812) exposure studies were submitted by the AEATF II.

The liquid pour study was designed to determine the dermal and inhalation exposures to occupational workers during manual open pouring of a non-volatile liquid containing an antimicrobial product.

Three different liquid pouring scenarios were considered in the study: use of conventional containers with no design modifications, reduced-splash or "no-glug" containers and pouring into a trigger spray bottle. The trigger spray bottle scenario was not considered relevant to paint-related manufacturing. Two non-volatile active ingredients, formulated as soluble concentrates, didecyl dimethyl ammonium chloride (DDAC) and C^{14}-alkyl dimethyl benzyl ammonium chloride (C^{14}-ADBAC) were used. The conventional and reduced-splash container scenarios included pouring a range of various amounts of active ingredient handled at different heights using various sized pouring and receiving containers. In this study, 18 subjects that performed 36 monitoring events (MEs) using the two surrogate active ingredients were monitored for dermal and inhalation exposures. Eighteen MEs poured DDAC, and eighteen MEs poured C^{14}-ADBAC. Each subject performed two MEs, one for pouring from a conventional container and the second from a reduced-splash container.

Container sizes were based on the typical product containers currently in the market. To account for different pouring heights, the receiving containers were placed randomly either on a table or on the floor. The receiving container sizes were variable as well and ranged from 3.785 or 7.571 L buckets to 189 L low-walled plastic troughs.

Subjects wore inner and outer cotton dosimeters. An air sampling pump was attached to the belt of the subject, and an OVS air sampling tube was placed in the subject's breathing zone. The face and the neck were wiped with gauze. Exposure to the rest of the head was extrapolated based on the ratio of the surface area of the face/neck to that of the rest of the head (all subjects were provided with safety glasses). Hand washes were conducted following the removal of the gloves; residues on the chemical-resistant gloves were not quantified. Total dermal exposure was calculated by summing the residues on the inner and outer dosimeters (based on the clothing scenario), face/neck wipes and hand wash samples for each monitoring event (ME). Inhalation unit exposure values were generated for workers performing light activity, not wearing respiratory protection.

To assess occupational exposure for scenarios where individuals handled conventional and reduced-splash containers, dermal unit exposure values were generated based on a single layer (long-sleeved shirt and long pants) plus chemical-resistant gloves. However, unit exposure values could not be generated for different levels of personal protective equipment, as exposure to the body was already minimal and below the level of quantification for most MEs. Therefore, adding additional protective equipment is not expected to significantly change exposure. The total dermal and inhalation unit exposure values for pouring from conventional containers and reduced-splash containers were presented as the AMu.

Similarly, the solid pour studies were designed to determine the dermal and inhalation exposures to occupational workers (primary handlers) when open pouring two different solid formulations (powder and granules) containing an antimicrobial.

Four different pouring scenarios were considered in this study. Two scenarios involved pouring powder and granular formulations in an occupational setting and the other two considered pouring powder and granular formulations in a residential setting. Study details are provided for the occupational scenarios only. The surrogate active ingredient used was cyanuric acid (1,3,5-triazine-2,4,6-triol, CAS number 108-80-5). Eighteen occupational workers poured the solid products into an indoor mix tank. Each subject was randomly assigned two monitoring numbers to account for two consecutive monitoring events, starting with the granules followed by the powder formulation to minimize the potential for cross contamination. All scenarios included manual pouring and/or scooping from different heights, using various sized containers.

Dermal exposure was measured using inner and outer cotton whole body dosimeters, hand washes, and face and neck wipes. All subjects were also given safety glasses and a dust mask. Subjects in the occupational scenario wore chemical-resistant gloves. Inhalation exposures were measured using IOM air sampling tubes (Institute of Occupational Medicine).

Separate dermal unit exposure values were generated for occupational workers wearing different levels of personal protective equipment. The inhalation unit exposure values for occupational handlers were generated for each individual performing light activities. The total dermal and inhalation unit exposure values were presented as the AMu of all test subjects.

For paint and building materials the unit exposure values from the liquid and solid pour studies were combined with the default amount of paint (used as a surrogate for building materials) treated per day (7571 L or 9388 kg based on paint density of 1.24 kg/L as a surrogate) by workers in manufacturing facilities to estimate exposures. For leather tanning solution, the unit exposure values from the same studies were combined with the default amount of product open-poured per day in a leather tanning facility (18.9 L per day) to estimate exposures. The amounts of paint treated per day and the amount of product open-poured for leather tanning per day were based on the USEPA Antimicrobial Division Draft Summary of Amounts Handled or Treated for Occupational Handler Scenarios.[1]

The risk assessment for primary handlers (mixers/loaders) is summarized in Appendix V, Table 1 (liquid open pour scenario) and Table 2 (solid, open pour scenario). Calculated MOEs for mixing/transfer of liquids and solids did not reach the target MOE for dermal and inhalation exposure, and, therefore, risks were not shown to be acceptable. To mitigate this risk, the following mitigation measures are proposed:

- Require closed transfer systems for liquid formulations.
- Require additional PPE (chemical-resistant coveralls and a respirator) for solid formulations coupled with a reduction in the amount handled per person per day (1.045 kg a.i./person/day).

[1] PMRA# 3084493. USEPA (2018). Summary of Amounts Handled or Treated for Occupational Handler Scenarios. EPA: Washington, DC.

5.2.2 Potential Risk to Postapplication Workers

Manufacturing facilities

Downstream postapplication workers in industrial settings are expected to be wearing PPE as required by law under occupational health and safety, which would limit potential exposure. Therefore, a quantitative risk assessment for downstream workers in industrial facilities involved with the manufacturing of paints and building materials (pigment dispersions, wallboard joint compounds, adhesives, mastics and latex caulks and vinyl wallboard pastes) was not conducted.

In leather tanning facilities, occupational postapplication exposure to diodofon can occur when voiding, cleaning and maintaining leather tanning drums and when removing freshly treated tanned leather skins from tanning drums prior to drying. In the absence of sufficient data to adequately assess the exposure from postapplication activities involving leather tanning, the use of diodofon in leather tanning operations is proposed for cancellation.

Secondary (Professional) Handlers

Exposure of workers (professional secondary handlers) to diodofon-treated paints and building materials were the postapplication occupational scenarios assessed for this special review.

Paint (Exterior and Interior) Uses

There is potential exposure for professional painters applying interior and exterior paints preserved with diodofon.

Exposure to diodofon in exterior paint is expected to be intermediate-term in duration (<180 days) while exposure to diodofon in interior paint is expected to be long-term in duration (that is, >180 days) via the dermal and inhalation routes.

Based on the use pattern, the following major scenarios were identified for professional painters:

- Applying paints using paint brush and roller; and
- Applying paints using an airless sprayer

The unit exposure values from the above brush and roller and airless sprayer exposure studies were combined with the default amounts of paint applied per day: 18.7 L per day (equivalent to 23.19 kg, based on paint density of 1.24 kg/L) using a brush and roller (2001 PMRA survey) and 120 L per day (equivalent to 232.5 kg, based on paint density of 1.24 kg/L) using an airless sprayer (PMRA# 2992785).

The risk assessment for professional painters is summarized in Appendix V, Table 3. When applying interior paints, calculated MOEs met the target MOEs when professional painters used a brush and roller. When using an airless sprayer, target MOEs were met only when wearing cotton coveralls over a single layer, chemical-resistant gloves, a painter's hat and a respirator.

When applying exterior paints, calculated MOEs met the target MOEs when professional painters used a brush and roller, When using an airless sprayer, target MOEs were met only when the maximum label rate is reduced to 1.8 g a.i./kg paint and painters wear cotton coveralls over a single layer, chemical-resistant gloves, painter's hat and a respirator. Nevertheless, as residential postapplication risks were not shown to be acceptable, it is proposed that the use of diodofon as a preservative in exterior paints be cancelled.

Pigment dispersions containing diodofon are likely to represent only a small component of the overall paint formulation. Therefore, secondary (professional) exposure to total diodofon residues in paint are not likely to represent a greater exposure than that determined for the paint use only.

Based on the findings of the paint transferable residue study, a quantitative occupational postapplication risk assessment for professional secondary handlers contacting treated surfaces for diodofon used in paint was not required.

Building Materials

In the case of building materials, no use description information was provided. Therefore, the default amount of paint handled per day by a professional painter (18.7 L or 23.19 kg) was used as a surrogate for the amount of building materials handled. Likewise, in the absence of a scenario-specific exposure study, the total body unit exposure values from the brush and roller study were used as a surrogate for applying building materials (except caulks and mastics).

For caulks and mastics, where the majority of the exposure is limited to the hands, in comparison to the exposure from applying other building materials (for example, adhesives), only the unit exposure values for the hands from the brush and roller study were considered for the risk assessment.

The risk assessment for workers applying building materials is summarized in Appendix V, Table 4. Using the appropriate unit exposure values from the brush and roller study, assuming the clothing scenario to be a long-sleeved shirt and long pants, together with the default amount handled, calculated MOEs did not meet the target MOE when applying building materials. To mitigate this risk, it is proposed that the rate of diodofon be reduced to 0.391 g a.i./kg product for building materials other than caulks and mastics. As this rate is lower than the lowest label rate for wallboard joint compounds, the use of diodofon in wallboard joint compounds is proposed for cancellation. For caulks and mastics, it is proposed that the rate of diodofon be reduced to 0.446 g a.i./kg product. However, considering the conservatisms (amount handled per day) and uncertainties (paint density as surrogate for building material density) in the postapplication risk assessment, the lowest label rate of 0.5 g a.i./kg product for mastics and caulks can be supported.

The likelihood of diodofon to leach out of dried caulks and adhesives (ceramic tile adhesives, vinyl wallpaper pastes), and mastics is expected to be very limited. This is further supported by the paint transferable residue studies, which demonstrated that the transfer of residues onto the skin following contact with a painted surface is minimal. Therefore transfer of, and dermal postapplication exposure to, diodofon residues is minimal and considered to be acceptable.

5.3 Aggregate Exposure and 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. Additionally, only exposures from routes that share common toxicological endpoints can be aggregated.

There are no registered diodofon food uses nor is it used in products designed for food packaging materials or in areas where food is stored, handled or processed. Therefore, an aggregate exposure and risk assessment is not required.

5.4 Cumulative Assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative effects of pest control products that have a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for diodofon. The toxicity exhibited following diodofon exposure in laboratory animals, including thyroid effects and certain reproductive effects that generally occurred at dose levels also resulting in thyroid toxicity, is thought to be due to excessive systemic iodine levels. Diodofon is comprised of 60% iodine by weight, with two iodine atoms that are rapidly cleaved from the diodofon molecule once absorbed. Iodine does not appear to be a major metabolite or a significant driver of toxicity via the dermal and inhalation routes for other currently registered pest control products. Of note is the antimicrobial iodocarb, which is comprised of 45% of iodine by weight and undergoes reductive dehalogenation as the first metabolic reaction in rats. While it is possible that iodine can be released from iodocarb and contribute to its toxicity, thyroid effects and reproductive toxicity were observed in laboratory animals only following oral dosing of iodocarb.

The effects observed in laboratory animals following dermal and inhalation exposure to iodocarb included portal of entry effects, decreased body weight gain, and cholinesterase inhibition and were unrelated to known iodine toxicity.

Overall, for the current evaluation, the PMRA did not identify information indicating that diodofon shares a common mechanism of toxicity with other pest control products for the relevant routes of exposure. Therefore, no cumulative health risk assessment is required at this time.

5.5 Incident Reports

As of 20 December 2019, no human or domestic animal incidents involving diodofon as a material preservative were submitted to the PMRA.

6.0 Proposed Special Review Decision for Diodofon

Evaluation of available scientific information related to the aspects of concern, indicated that the potential risk to human health (potential applicator and postapplication risks) from diodofon is considered to be acceptable with the following proposed risk mitigation measures (see below and Appendix VII). On this basis, Health Canada is proposing that products containing diodofon used as a material preservative are acceptable for continued registration in Canada with the proposed risk mitigation measures pursuant to subsection 21(1) of the *Pest Control Product Act*.

To mitigate risks to individuals using diodofon as a material preservative or handling diodofon-treated products:

For primary handlers (mixers/loaders) working in manufacturing facilities:

- Require closed transfer systems for liquid formulations
- Require additional PPE (chemical-resistant coveralls and a respirator) for solid formulations and a reduction in the amount handled per person per day (1.045 kg a.i./person/day).

For secondary professional handlers applying interior paints using an airless sprayer:

- Require additional protective equipment (chemical-resistant gloves, cotton coveralls, a painter's hat and a respirator) coupled with an outreach/stewardship program.

For secondary handlers (downstream-industrial, professional and/or residential):

- Reduction of the maximum application rate for uses in building materials (except caulks and mastics) to 0.391 g a.i./kg product and to 0.50 g a.i./kg product for caulks and mastics
- Cancel the use of diodofon in wallboard joint compound
- Cancel the use of diodofon in exterior paints
- Cancel the use of diodofon in leather tanning

This proposed special review decision is a consultation document.[2] Health Canada will accept written comments on this proposal up to 90 days from the date of publication of this document. Please forward all comments to PMRA Publications (please see contact information on the cover page of this document).

7.0 Next Steps

Before making a special review decision on diodofon, Health Canada will consider all comments received from the public in response to this consultation document. A science-based approach will be applied in making a final decision on diodofon. Health Canada will then publish a special review decision document, which will include the decision, the reasons for it, a summary of the comments received on the proposed decision and Health Canada's response to these comments.

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

8.0 Additional Scientific Information

No additional scientific data are being requested. However, during the consultation period, the registrants and other stakeholders may consider submitting the following information that may address uncertainties in the available information database of diodofon and support refined risk assessment. In addition, stakeholders may consider providing information on risk management options for diodofon (for example, additional PPE, engineering controls).

The evaluation of any additional data would be based on the scientific merit and relevance to the risk assessment. While additional data may reduce uncertainty in the risk assessment, continued registration of any uses would be based on the acceptability of risk assessed using a science-based approach.

Additional detailed use description information and other data/information that may allow further refinement of the risk assessment:

- Refined daily amounts of paint manufactured and treated with preservatives in Canada
- Actual daily amounts of paint-related uses/building materials treated with preservatives and handled by professional secondary handlers
- Chemical-specific dermal absorption studies conducted with diodofon-treated paint formulations
- Passive-dosimetry data for the occupational postapplication exposure incurred during leather tanning (that is, downstream industrial activities)

List of Abbreviations

µg	microgram
µL	microlitre
a.i.	active ingredient
AEATF II	Antimicrobial Exposure Assessment Task Force II
AMu	geometric mean based on the arithmetic mean
ARI	aggregate risk index
AST	aspartate aminotransferase
BIT	1,2-benzisothiazolin-3-one
bw	body weight
bwg	bodyweight gain
ADBAC	alkyl dimethyl benzyl ammonium chloride
DDAC	didecyl dimethyl ammonium chloride
g	gram(s)
IT	intermediate-term
kg	kilogram(s)
L	litre(s)
LT	long-term
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
m^2	square metre
ME	monitoring events
mg	milligram(s)
min	minute(s)
mL	millilitre(s)
MOE	margin of exposure
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PON	propiconazole
PPE	personal protective equipment
PRVD	Proposed Re-evaluation Decision
RED	Reregistration Eligibility Decision
REV	Re-evaluation Note
RVD	Re-evaluation Decision
SOP	Standard operating procedure
T3	serum triiodothyronine
TSH	thyroid stimulating hormone
USEPA	United States Environmental Protection Agency
WBC	white blood cells
WP	wettable powder
wt	weight

Appendix I Registered products containing diodofon as of 9 January 2020

Registration Number	Marketing Class	Registrant	Product Name	Formulation	Guarantee
15320	T	3313045 Nova Scotia Company	Amicale Technical		93.15%
15321	C	3313045 Nova Scotia Company	Amical Flowable (Antimicrobial Agent)	Suspension	39.2%
22910	C	3313045 Nova Scotia Company	Amical WP (Antimicrobial Powder)	Powder	47.5%
27102	C	3313045 Nova Scotia Company	Amical 48 (Antimicrobial Powder)	Dust	93.15%
25848	C	Thompson Research Associates Canada Inc.	Ultra-Fresh 40	Suspension	39.2%
25887	C	Thompson Research Associates Canada Inc.	Ultra-Fresh 95	Dust	93.5%

T = technical grade active ingredient; C = commercial
Note: Discontinued products and products with submissions for discontinuation not included.

Appendix II Studies Submitted by the Registrant(s) under section 12 of the *Pest Control Products Act*

Table 1 Following the re-evaluation of Diodofon, the PMRA received the following studies under section 12 of the *Pest Control Products Act.*

PMRA Document Number	Study Title
2243749	2010. Amical 48: 28-Day Dermal Toxicity Study in Crl:CD(SD) Rats. DACO 4.3.5
2243750	2011. Amical 48 Antifungal Agent: 90-Day Inhalation Toxicity Study in Crl:CD(SD) Rats. DACO 4.3.6
2243751	2012. Product Use Descriptions - Amical 48. DACO 5.2
2243752, 2243753, 2243754 and 2243755	2008. Risk Characterisation for the use of the active substance in biocidal product: p-[(Diiodomethyl) sulphonyl]toluene in AMICA 48 Antimicrobial. DACO 5.2
2243756	2008. Di-iodomethyl-p-tolyl sulfone: determination of the leaching rate from wood following a simulated pressure treatment. DACO 5.9

Appendix III Toxicology Summary Tables

Table 1 New Toxicology Studies for Diodofon*

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ weights unless otherwise noted.

Study Type/ Animal/ PMRA #	Study Results
Short-Term Toxicity Studies	
28-Day Dermal Toxicity Sprague-Dawley rats PMRA #2243749	**Dermal NOAEL = 20 mg/kg bw/day** **Systemic NOAEL (♀) = 20 mg/kg bw/day** **Systemic LOAEL (♂) = 20 mg/kg bw/day** ≥20 mg/kg bw/day: histologic changes in the thyroid (very slight follicular cell hypertrophy, very slight altered tinctorial properties) (♂) ≥100 mg/kg bw/day: slight epidermal hyperplasia, focal or multifocal parakeratosis (♂/♀); slight ↑ AST, very slight erythema, scabs of varying severities, slight to severe scaling, small scabs at the dermal test site, slight multifocal epidermal ulceration, histologic changes in the thyroid (very slight follicular cell hypertrophy, very slight altered tinctorial properties) (♀) 500 mg/kg bw/day: subacute to chronic inflammation in the dermis, very slight and slight edema, ↑ thyroid wt (♂/♀); multifocal epidermal ulceration, small scabs at the dermal test site, scratches in thoracic region (♂); ↑ WBC, ↑ neutrophils, myeloid cell hyperplasia in bone marrow, extramedullary hematopoiesis in spleen (♀)
90-Day Inhalation Toxicity Sprague-Dawley rats PMRA #2243750	**NOAEC = 0.001 mg/L (0.26 mg/kg bw/day)** ≥0.001 mg/L (0.26 mg/kg bw/day): ↑ neutrophils (♂) [not considered adverse at this dose level] ≥0.007 mg/L (12.8 mg/kg bw/day): parakeratosis and inflammation of ventral meatus, altered tinctorial properties of colloid in thyroid (♂/♀); one mortality, squamous metaplasia of respiratory epithelium lining of ventral meatus and nasal septum (♂); olfactory epithelium degeneration (♀) 0.03 mg/L (235 mg/kg bw/day): laboured breathing, incoordination, perinasal soiling, five mortalities (4♂/1♀), ↑ lung wt, multifocal chronic active inflammation of alveolar septa, slight multifocal degeneration of nasolacrimal duct, moderate to severe necrosis of the laryngeal mucosa (♂/♀); ↓ bw, ↓ bwg, ↑ WBC, olfactory epithelium degeneration, respiratory epithelium degeneration, erosion/ulceration of ventral meatus, moderate to severe multifocal necrotizing bronchioalveolar inflammation, autolysis of thyroid tissue (♂); ↓ lymphocytes, ↑ neutrophils, squamous metaplasia of respiratory epithelium lining of ventral meatus and nasal septum, diffuse fibrinopurulent necrotizing inflammation in trachea (♀)

*Refer to PMRA# 2542814 for summary of additional toxicity studies.

Table 2 Toxicology Reference Values for Use in Health Risk Assessment for Diodofon

Exposure Scenario	Study	Point of Departure and Endpoint	Target MOE
Short- and intermediate-term dermal	28-day dermal toxicity in rats	LOAEL of 20 mg/kg bw/day based on minor histological changes in the thyroid	100
Long-term dermal	28-day dermal toxicity in rats	LOAEL of 20 mg/kg bw/day based on minor histological changes in the thyroid	1000
Short- and intermediate-term inhalation	90-day inhalation toxicity in rats	NOAEL of 0.26 mg/kg bw/day (0.001 mg/L) based on histological effects in the thyroid, nasal and respiratory tissues at 13 mg/kg bw/day (0.007 mg/L)	100
Long-term inhalation	90-day inhalation toxicity in rats	NOAEL of 0.26 mg/kg bw/day (0.001 mg/L) based on histological effects in the thyroid, nasal and respiratory tissues at 13 mg/kg bw/day (0.007 mg/L)	300

Appendix IV Residential Exposure and Risk Assessments

Table 1 Residential Painting Exposure and Risk Assessment (Short-Term)

Product Type	Scenario	Application rate (g a.i./kg paint)[a]	Amount handled per day (g a.i./day)[b]	Unit exposure value[c] (µg/kg a.i.)		Daily exposure[d] (mg/kg bw/day)		Margin of exposure (MOE)[e]		
				Dermal	Inhalation	Dermal	Inhalation	Dermal[f]	Inhalation[g]	Combined[h]
Shorts, short-sleeved shirt, no gloves										
Exterior Paints	Brush and roller	3	28.20	237445	17.30	0.08	0.000006	239	42639	238
		1.8	16.92	237445	17.30	0.05	0.000004	398	71065	396
	Airless sprayer	3	211	196244	2169	0.52	0.006	39	45	21
		1.8	127	196244	2169	0.310	0.003	64	76	35
Interior Paints	Brush and roller	0.263	2.47	237445	17.30	0.01	0.0000005	2726	486374	2711
	Airless sprayer	0.263	18.49	196244	2169	0.05	0.0005	441	519	238

Shaded cells indicate where the MOE is less than the target MOE (100)

[a] Application rate = As listed on registered labels (exterior paint: 3 g a.i./kg paint (max) and 1.8 g a.i./kg paint (min); interior paint: 0.263 g a.i./kg paint)

[b] Amount handled per day for each type of painting equipment = Application rate × amount of paint applied/day (7.58 L using brush and roller and 56.7 L using airless sprayer) × paint density (1.24 kg/L)

[c] Unit exposure values from AEATF II brush and roller and airless sprayer studies

[d] Daily exposure = [Amount handled per day × Unit exposure value × Absorption × CF (1 mg/1000 µg) × CF (1 kg/1000 g)]/80 kg bw. Absorption not required for dermal exposure; 100% absorption for inhalation exposure.

[e] Dermal MOE = LOAEL/dermal daily exposure; inhalation MOE = NOAEL/ inhalation daily exposure

[f] Dermal LOAEL of 20 mg/kg bw/day from a rat dermal toxicology study and target MOE of 100.

[g] Inhalation NOAEL of 0.26 mg/kg bw/day from a rat inhalation study and target MOE of 100.

[h] Combined MOE = $1/((1/MOE_{Dermal}) + (1/MOE_{Inhalation}))$

Table 2 Residential Exposure and Risk Assessment from Applying Building Materials Using Brush and Roller (Short-Term)

Product Type	Application rate (g a.i./kg product)[a]	Amount handled per day (g a.i./day)[b]	Unit exposure value[c] (µg/kg a.i.)		Daily exposure[d] (mg/kg bw/day)		Margin of exposure (MOE)[e]		
			Dermal	Inhalation	Dermal	Inhalation	Dermal[f]	Inhalation[g]	Combined[h]
Shorts, short-sleeved shirt, no gloves									
Adhesives	1.5	14.10	237445	17.30	0.04	0.000003	478	85278	475
Vinyl wallboard pastes	1.2	9.10	237445	17.30	0.03	0.000002	741	132180	737
Wallboard joint compounds	3	28.20	237445	17.30	0.05	0.000006	239	42639	238
Caulking	3	28.20	154209	17.30	0.05	0.000006	368	42639	365
Mastics	1.5	14.10	154209	17.30	0.03	0.000003	736	85278	730

Shaded cells indicate where the MOE is less than the target MOE (100)

[a] Application rate = Maximum rates listed on all registered labels.

[b] Amount handled per day for each type of painting equipment = Application rate × amount of building material applied/day (7.58 L using brush and roller) × paint density (1.24 kg/L; surrogate for building materials)

[c] Unit exposure values from AEATF II brush and roller study

[d] Daily exposure = [Amount handled per day × Unit exposure value × Absorption × CF (1 mg/1000 µg) × CF (1 kg/1000 g)]/80 kg bw. Absorption not required for dermal exposure; 100% absorption for inhalation exposure.

[e] Dermal MOE = LOAEL/dermal daily exposure; inhalation MOE = NOAEL/inhalation daily exposure

[f] Dermal LOAEL of 20 mg/kg bw/day from a rat dermal toxicology study and target MOE of 100.

[g] Inhalation NOAEL of 0.26 mg/kg bw/day from a rat inhalation study and target MOE of 100.

[h] Combined MOE = $1/((1/MOE_{Dermal}) + (1/MOE_{Inhalation}))$

Appendix V Occupational Exposure and Risk Assessments

Table 1 Occupational Long-Term Exposure and Risk Assessment for Use of Diodofon in Manufacturing Facilities Using Liquid, Open Pour Scenario

Use	Application rate (g a.i./kg product)[a]	Amount handled per day (g a.i./day)[b]	Unit exposure value[c] (µg/kg a.i.)		Daily exposure[d] (mg/kg bw/day)		Margin of Exposure (MOE)[e]		Aggregate Risk Index (ARI)
			Dermal	Inhalation	Dermal	Inhalation	Dermal[f]	Inhalation[g]	
Cotton coveralls over single layer, chemical-resistant gloves									
Exterior paint, caulking and wallboard joint compounds	3	28163	1922	5.08	0.677	0.002	30	145	0.03
Interior Paint	0.25	2375	1922	5.08	0.057	0.0002	350	1723	0.33
Pigment dispersions, mastics and adhesives	1.5	14082	1922	5.08	0.338	0.0009	59	291	0.06
Vinyl wallboard pastes	1.2	11265	1922	5.08	0.271	0.0007	74	363	0.07
Leather	2.94	9831	1922	5.08	0.236	0.0006	85	416	0.08

Shaded cells indicate where the MOE is less than the target MOE (dermal: 1000; inhalation: 300) or ARI is less than 1

[a] Application rate = As listed on all registered labels

[b] Amount handled per day for leather = Amount of end-use product (EP) open poured per day (18.9 L) x guarantee (% w/w) x density of EP; Amount handled per day for other uses = Application rate × amount of paint or building materials treated/day (7571 L) × paint density (1.24 kg/L; surrogate for building materials)

[c] Unit exposure values from AEATF II liquid, open pour study

[d] Daily exposure = [Amount handled per day × Unit exposure value × Absorption × CF (1 mg/1000 µg) × CF (1 kg/1000 g)]/80 kg bw. Absorption not required for dermal exposure; 100% absorption for inhalation exposure.

[e] Dermal MOE = LOAEL/dermal daily exposure; inhalation MOE = NOAEL/inhalation daily exposure

[f] Dermal LOAEL of 20 mg/kg bw/day from a rat dermal toxicology study and target MOE of 1000.

[g] Inhalation NOAEL of 0.26 mg/kg bw/day from a rat inhalation study and target MOE of 300.

[h] ARI = $1/((\text{Target MOE}_{\text{Dermal}}/\text{MOE}_{\text{Dermal}}) + (\text{Target MOE}_{\text{Inhalation}}/\text{MOE}_{\text{Inhalation}}))$

Table 2 Occupational Long-Term Exposure and Risk Assessment for Use of Diodofon in Manufacturing Facilities Using Solid (Dust), Open Pour Scenario

Use	Application rate (g a.i./kg product)[a]	Amount handled per day (g a.i./day)[b]	Unit exposure value[c] (µg/kg a.i.)		Daily exposure[d] (mg/kg bw/day)		Margin of Exposure (MOE)[e]		Aggregate Risk Index[h] (ARI)
			Dermal	Inhalation	Dermal	Inhalation	Dermal[f]	Inhalation[g]	
Cotton coveralls over single layer, chemical-resistant gloves									
Exterior paint, caulking and wallboard joint compounds	3	28163	366	575.71	0.129	0.203	155	1	0.004
Interior paint	0.263	2469	366	575.71	0.011	0.018	1771	15	0.05
Pigment dispersions, mastics and adhesives	1.5	14082	366	575.71	0.064	0.101	310	3	0.01
Vinyl Wallboard Pastes	1.2	11265	366	575.71	0.052	0.081	388	3	0.01
Leather	2.79	14986	366	575.71	0.069	0.108	292	2	0.01
Chemical-resistant coveralls over single layer, chemical-resistant gloves, respirator									
Exterior paint, caulking and wallboard joint compounds	3	28163	198	57.57	0.070	0.020	287	13	0.04
Interior paint	0.263	2469	198	57.57	0.006	0.002	3273	146	0.42
Pigment Dispersions, Mastics and Adhesives	1.5	14082	198	57.57	0.035	0.010	574	26	0.07
Vinyl Wallboard Pastes	1.2	11265	198	57.57	0.028	0.008	717	32	0.09
Leather	2.79	14986	198	57.57	0.037	0.011	539	24	0.07
Chemical-resistant coveralls over single layer, chemical-resistant gloves, respirator									
All uses	n/a	1045	198	57.57	0.0026	0.0008	7731	346	1

Shaded cells indicate where the MOE is less than the target MOE (dermal: 1000; inhalation: 300) or ARI is less than 1

[a] Application rate = Maximum rates as listed on all registered labels

[b] Amount handled per day for leather = Amount of end-use product (EP) open poured per day (18.9 L) x guarantee (% w/w) x density of EP
Amount handled per day for other uses = Application rate × amount of paint or building materials treated/day (7571 L) × paint density (1.24 kg/L; surrogate for building materials). The maximum allowable amount of a.i. handled per day per person for MOEs to be acceptable is 1045 g a.i./day.

[c] Unit exposure values from AEATF II solid, open pour study

[d] Daily exposure = [Amount handled per day × Unit exposure value × Absorption × CF (1 mg/1000 µg) × CF (1 kg/1000 g)]/80 kg bw. Absorption not required for dermal exposure; 100% absorption for inhalation exposure.

[e] Dermal MOE = LOAEL/dermal daily exposure; inhalation MOE = NOAEL/inhalation daily exposure

[f] Dermal LOAEL of 20 mg/kg bw/day from a rat dermal toxicology study and target MOE of 1000.

[g] Inhalation NOAEL of 0.26 mg/kg bw/day from a rat inhalation study and target MOE of 300.

[h] ARI = $1/((\text{Target MOE}_{\text{Dermal}}/\text{MOE}_{\text{Dermal}}) + (\text{Target MOE}_{\text{Inhalation}}/\text{MOE}_{\text{Inhalation}}))$

Table 3 Professional Painter Exposure and Risk Assessment for Exterior Paints (Intermediate term (IT)) and Interior Paints (Long term (LT))

Product Type	Scenario	Application rate (g a.i./kg product)a	Amount handled per day (g a.i./day)b	Unit exposure valuec (µg/kg a.i.)		Daily exposured (mg/kg bw/day)		Margin of Exposure (MOE)e		
				Dermal	Inhalation	Dermal	Inhalation	Dermalf	Inhalationg	Combinedh
Exterior Paints (IT)	Single layer, no gloves									
	Brush and roller	3	70	175871	17.3	0.153	0.00002	131	17284	130
		1.8	42	175871	17.3	0.092	0.000009	218	28806	216
	Airless sprayer	3	446	65937	2169	0.368	0.0121	54	21	15
		1.8	268	65937	2169	0.310	0.0102	65	26	18
	Cotton coveralls over single layer, chemical-resistant gloves, painter's hat, respirator									
	Airless sprayer	1.8	268	7402	217	0.025	0.0007	807	358	248
Product Type	Scenario	Application rate (g a.i./kg product)a	Amount handled per day (g a.i./day)b	Unit exposure valuec (µg/kg a.i.)		Daily exposured (mg/kg bw/day)		Margin of Exposure (MOE)e		Aggregate Risk Index (ARI)i
				Dermal	Inhalation	Dermal	Inhalation	Dermalf	Inhalationg	
Interior Paints (LT)	Single layer, no gloves									
	Brush and roller	0.263	6	175871	17.3	0.013	0.000001	1492	197151	1.5
	Airless sprayer	0.263	39	65937	2169	0.032	0.0011	620	245	0.4
	Cotton coveralls over single layer, chemical-resistant gloves, painter's hat, respirator									
	Airless sprayer	0.263	39	7402	217	0.004	0.0001	5523	2450	3.3

Shaded cells indicate where the MOE is less than the target MOE (dermal: IT – 100, LT – 1000; inhalation: IT – 100, LT – 300)

[a] Application rate = As listed on registered labels (exterior paint: 3 g a.i./kg paint (max) and 1.8 g a.i./kg paint (min); interior paint: 0.263 g a.i./kg paint)

[b] Amount handled per day for each type of painting equipment = Application rate × amount of paint applied/day (18.7 L using brush and roller and 120 L for airless sprayer) × paint density (1.24 kg/L)

[c] Unit exposure values from AEATF II brush and roller and airless sprayer studies

[d] Daily exposure = [Amount handled per day × Unit exposure value × Absorption × CF (1 mg/1000 µg) × CF (1 kg/1000 g)]/80 kg bw. Absorption not required for dermal exposure; 100% absorption for inhalation exposure.

[e] Dermal MOE = LOAEL/dermal daily exposure; inhalation MOE = NOAEL/inhalation daily exposure

[f] Dermal LOAEL of 20 mg/kg bw/day from a rat dermal toxicology study and target MOE of 100 (intermediate-term) and 1000 (long-term).

[g] Inhalation NOAEL of 0.26 mg/kg bw/day from a rat inhalation study and target MOEs of 100 (intermediate-term) and 300 (long-term).

[h] Combined MOE = $1/((1/MOE_{Dermal}) + (1/MOE_{Inhalation}))$

[i] ARI = $1/((\text{Target } MOE_{Dermal}/MOE_{Dermal}) + (\text{Target } MOE_{Inhalation}/MOE_{Inhalation}))$

Table 4 Professional Worker Long-Term Exposure and Risk Assessment from Applying Building Materials Using Brush and Roller

Product Type	Application rate (g a.i./kg product)[a]	Amount handled per day (g a.i./day)[b]	Unit exposure value[c] (µg/kg a.i.)		Daily exposure[d] (mg/kg bw/day)		Margin of exposure (MOE)[e]		Aggregate Risk Index (ARI)[h]
			Dermal	Inhalation	Dermal	Inhalation	Dermal[f]	Inhalation[g]	
Single layer, no gloves; Application rate = maximum label rate									
Adhesives	1.5	35	175871	17.3	0.0765	0.00001	262	34567	0.26
Vinyl wallboard pastes	1.2	28	175871	17.3	0.0612	0.00001	327	43209	0.33
Wallboard joint compounds	3	70	175871	17.3	0.1529	0.00002	131	17284	0.13
Caulking	3	70	154209	17.3	0.1341	0.00002	149	127284	0.15
Mastics	1.5	35	154209	17.3	0.0670	0.00001	298	34567	0.30
Single layer, no gloves; Reduced maximum application rate									
Adhesives, vinyl wallboard pastes, and wallboard joint compounds	0.391	9.1	175871	17.3	0.020	0.000002	1003	132610	1
Caulking and mastics	0.446	10	154209	17.3	0.020	0.000002	1003	116257	1

Shaded cells indicate where the MOE is less than the target MOE (dermal: 1000; inhalation: 300)

[a] Application rate = Maximum rates as listed on all registered labels. Reduced application rates (0.391 g a.i./kg and 0.446 g a.i./kg) reflect rates that were shown to be acceptable; note that the acceptable rate for wallboard joint compounds is lower than the lowest registered label rate of 0.8 g a.i./kg product.

[b] Amount handled per day for each type of building material = Application rate × amount of building materials applied/day (18.7 L using brush and roller) × paint density (1.24 kg/L; surrogate for building materials)

[c] Unit exposure values from AEATF II brush and roller study

[d] Daily exposure = [Amount handled per day × Unit exposure value × Absorption × CF (1 mg/1000 µg) × CF (1 kg/1000 g)]/80 kg bw. Absorption not required for dermal exposure; 100% absorption for inhalation exposure.

[e] Dermal MOE = LOAEL/dermal daily exposure; inhalation MOE = NOAEL/inhalation daily exposure

[f] Dermal LOAEL of 20 mg/kg bw/day from a rat dermal toxicology study and target MOE of 1000.

[g] Inhalation NOAEL of 0.26 mg/kg bw/day from a rat inhalation study and target MOE of 300.

[h] ARI = $1/((\text{Target MOE}_{\text{Dermal}}/\text{MOE}_{\text{Dermal}}) + (\text{Target MOE}_{\text{Inhalation}}/\text{MOE}_{\text{Inhalation}}))$

Appendix VI Proposed Label Amendments and New Labelling Required for Products Containing Diodofon

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

The following uses are proposed for cancellation. All references to these uses must be removed from all end-use product labels:

- Exterior latex paint
- Wallboard joint compound
- Leather tanning

The following product is proposed for cancellation, as leather tanning is the only registered use on the label:

- Amical WP (Antimicrobial Powder) [PCP# 22910]

1.0 Label Amendments for Commercial Class End-use Products Containing Diodofon

Label statements must be amended (or added) to include the following directions to the appropriate labels, unless the current label mitigation is more restrictive:

2.0 PRECAUTIONS

2.1 Personal Protective Equipment

2.1.1 Suspensions – PCP#s 15321 and 25848

Use a closed transfer system when mixing and loading.

2.1.2 Dusts and Powders – PCP#s 27102 and 25887

Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and chemical-resistant footwear and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides during mixing, loading, clean-up and repair.

Limit the amount of active ingredient handled to 1.045 kg per person per day. These restrictions are in place to minimize exposure to individual handlers. Application may need to be performed over multiple days or by using multiple handlers.

2.1.3 Manufactured paint products (EPs) containing the preservative diodofon must be labelled with the following information:

Professional painters USING AN AIRLESS SPRAYER must wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, a painter's hat, and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides during paint application.

3.0 DIRECTIONS FOR USE FOR ALL PRODUCTS

Reduce the maximum application rates for caulks and mastics to 0.5 g a.i./kg.

Reduce the maximum application rates for adhesives and vinyl wallboard pastes to 0.391 g a.i./kg.

References

Published Information

PMRA Document Number	Reference
1880445	Canada, 2010a. Pest Management Regulatory Agency. Proposed Re-evaluation Decision Document PRVD 2010-04, *Diodofon*. March 19, 2010.
1978869	Canada, 2010b. Pest Management Regulatory Agency. Re-evaluation Decision RVD 2010-13, *Diodofon*. October 19, 2010.
2662491	Canada, 2016. Pest Management Regulatory Agency. Section 18(1) Notice Announcement for Initiation of Special Review, Active Ingredient: Diodofon. Reference Number: 2016-3404. July 22, 2016.
2542814	USEPA, 2008. Reregistration Eligibility Decision (RED) Document for Diiodomethyl p-tolyl sulfone. U.S. Environmental Protection Agency, Washington, DC. March 31, 2008.
2409268	US EPA, 2012. Standard Operating Procedures for Residential Pesticide Exposure Assessment. USEPA Office of Prevention, Pesticides and Toxic Substances: Washington, DC. Revised October 2012. DACO: 12.5.5. Section 10.

Unpublished Information

PMRA Document Number	Reference
2243749	2010. Amical 48: 28-Day Dermal Toxicity Study in Crl:CD(SD) Rats. 15 June 2010. DACO: 4.3.5
2243750	2011. Amical 48 Antifungal Agent: 90-Day Inhalation Toxicity Study in Crl:CD(SD) Rats.29 November, 2011. DACO: 4.3.6
2243751	2012. Product Use Descriptions: Amical 48 (Diiodomethyl p-tolyl sulfone). October 22, 2012. DACO: 5.2
2243752	2012. Risk Characterisation for the Use of the Active Substance in Biocidal Product P-[(Diiodomethyl) Sulphonyl] Toluene In Amical 48 Antimicrobial. October 22, 2012. DACO: 5.2
2243753	2012. Risk Characterisation For The Use Of The Active Substance In Biocidal Product P-[(Diiodomethyl) Sulphonyl] Toluene In Amical 48 Antimicrobial (Part 7). October 22, 2012. DACO: 5.2
2243754	2012. Risk Characterisation For The Use Of The Active Substance In Biocidal Product P-[(Diiodomethyl) Sulphonyl] Toluene In Amical 48 Antimicrobial (Part 9). October 22, 2012. DACO: 5.2
2243755	2012. Risk Characterisation For The Use Of The Active Substance In Biocidal Product P-[(Diiodomethyl) Sulphonyl] Toluene In Amical 48 Antimicrobial (Part 10). October 22, 2012. DACO: 5.2

AEATF II Studies:

PMRA Document Number	Reference
2834812	A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of Two Solid Formulations Containing an Antimicrobial. American Chemistry Council, Antimicrobial Exposure Assessment Task Force II, Washington, DC. (AEATF II) Project ID: AEA07.
2296582	A Study for Measurement of Potential Dermal and Inhalation Exposure during Manual Pouring of a Liquid Containing an Antimicrobial. American Chemistry Council, Antimicrobial Exposure Assessment Task Force II, Washington, DC. (AEATF II) Project ID: AEA05.
2849401	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. Antimicrobial Exposure Assessment Task Force II (AEATF II), Washington, DC. January 31, 2018 Project ID: AEA09.
3003682	A Study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial using an Airless Sprayer. American Chemistry Council, Antimicrobial Exposure Assessment Task Force II, Washington, DC. (AEATF II) Project ID: AEA10.
2967976	Analysis of Propiconazole Used as an In-Can Paint Preservative in Wall Wipe Samples Collected from Dried Paint During An Airless Paint Monitoring Study. American Chemistry Council, Antimicrobial Exposure Assessment Task Force II (AEATF II). (AEATF II) Project ID: AEA10.
2883917	Analysis of 1,2-Benzisothiazolin-3-one (BIT) in Background Wall Wipe Samples from Indoor Wall Surfaces Painted with Latex Paint Using a Brush and Roller (Non-GLP). Antimicrobial Exposure Assessment Taskforce II (AEATF II), Washington, DC. (AEATF II) Project ID: AEA19.
2296584	A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of a Liquid Containing an Antimicrobial. Supplemental Report – Supplement 1, Antimicrobial Exposure Assessment Task Force II, Washington, DC. (AEATF II) Project ID: AEA05.
2992785	2017, Study Design: A Study for Measurement of Potential Dermal and Inhalation Exposure During the Application of Paint Containing an Antimicrobial using an Airless Sprayer. American Chemistry Council, Antimicrobial Exposure Assessment Task Force II, Washington, DC. (AEATF II) Project ID: AEA10.