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Proposed Special Review Decision PSRD2024-02

Proposed Special Review Decision for the Metalworking Fluid Uses of Iodocarb and Its Associated End-use Products

Consultation Document

(publié aussi en français)

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Proposed special review decision for iodocarb (3-iodo-2-propynyl butyl carbamate) and its associated end-use products

Under the authority of the *Pest Control Products Act*, pesticides are regulated by Health Canada's Pest Management Regulatory Agency (PMRA) on behalf of the Minister of Health. The *Pest Control Products Act* prescribes both the pre-market and post-market assessment (re-evaluations and special reviews) of pesticides to determine the acceptability or continued acceptability of human health and environmental risks, and acceptable value of a pesticide in Canada. Unlike a re-evaluation, a special review is triggered only under certain circumstances, as described in section 17 of the *Pest Control Products Act*, and the intent of a special review is to address specifically the identified aspect(s) of concern. The special review approach is described in the PMRA Guidance Document: *Approach to Special Reviews of Pesticides*.

Health Canada evaluates the aspect(s) of concern that prompted the special review in accordance with subsection 18(4) of the *Pest Control Products Act*. The internationally accepted science-based approach is used for the assessment of the aspect(s) of concern, similar to all other scientific assessments (for example, new product registrations, re-evaluations). This step includes both risk (or value, if applicable) assessment and risk management to address the concerns identified. Health Canada's approach to risk and value assessment as well as risk management is outlined in the *Framework for Risk Assessment and Risk Management of Pest Control Products*.[1]

Pursuant to subsection 17(1) of the *Pest Control Products Act*, Health Canada initiated a special review of registered pest control products containing iodocarb (3-iodo-2-propynyl butyl carbamate) used in metalworking fluids. This special review was initiated based on post application exposure information, relating to workers handling iodocarb-treated metalworking fluids and/or involved in maintenance/clean-up activities, submitted under section 12 of the *Pest Control Products Act*. These section 12 data were required as a result of the re-evaluation of iodocarb (RVD2011-04)[2]. The identified aspect of concern is:

- Potential occupational dermal risk to workers exposed to iodocarb-treated metalworking fluids.

During the assessment of the above aspect of concern, additional potential health concerns were identified, which led to the expansion of the scope of this special review as per subsection 17(7) of the *Pest Control Products Act*. Therefore, the overall aspects of concern for this special review are:

- Potential dermal and inhalation risks of concern for mixers/loaders treating metalworking fluids with iodocarb.

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1 PMRA Guidance Document, *A Framework for Risk Assessment and Risk Management of Pest Control Products*

2 RVD2011-04. *Re-evaluation Decision for Iodocarb*.

- Potential dermal and inhalation risks of concern for secondary workers (machinists) exposed to iodocarb-treated metalworking fluids.

Pursuant to subsection 18(4) of the *Pest Control Products Act*, Health Canada has evaluated the aspects of concern within the scope of this special review, which are relevant to human health, for registered pest control products containing iodocarb used in metalworking fluids.

Iodocarb is an antimicrobial used as a material preservative (including paints, adhesives and caulks, paper coating, plastic, textiles, and liquid detergents) and industrial fluids preservative (metalworking fluids). It is also used as a joinery wood preservative and sapstain control chemical. For this special review, currently registered products containing iodocarb that are used as preservatives in metalworking fluids were considered and are listed in Appendix I.

This document presents the proposed special review decision for iodocarb, including the proposed amendments (risk mitigation measures) to protection human health, as well as the science evaluation on which the proposed special review decision is based. All products containing iodocarb used in metalworking fluids that are registered in Canada are subject to this proposed special review decision. This document is subject to a 45-day public consultation period[3] during which the public (including the pesticide manufacturers and stakeholders) may submit written comments and additional information to PMRA Publications. The final special review decision will be published after taking into consideration the comments and information received during the consultation period.

Proposed special review decision for iodocarb

Health Canada, under the authority of the *Pest Control Products Act*, has conducted an evaluation of available relevant scientific information related to the aspects of concern for human health in accordance with subsection 18(4) of the *Pest Control Products Act*. Based on the evaluation of the aspects of concern, Health Canada is proposing for public consultation, pursuant to section 28 of the *Pest Control Products Act*, the continued registration of iodocarb used in metalworking fluids and its associated end-use products registered for sale and use in Canada under section 21 of the *Pest Control Products Act*.

The evaluation of available relevant scientific information related to the aspects of concern indicated that iodocarb used in metalworking fluids showed acceptable risk when iodocarb is used according to the proposed conditions of registration, which includes new mitigation measures.

The proposed additional mitigation measures are summarized below, and details are outlined in Appendix V.

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

Risk mitigation measures

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment and must be followed by law. The proposed label amendments including any revised/updated label statements and/or mitigation measures, as a result of the special review of iodocarb, are summarized below. Refer to Appendix V for details.

Human health

To protect workers (mixers/loaders) from exposure when treating metalworking fluids with iodocarb:

- When open pouring products containing iodocarb into metalworking fluid, the proposed maximum amount of iodocarb handled per day is limited to 1.25 kg a.i./person. If handling more than this, a closed transfer (injection) system is required.

To protect secondary workers (machinists) from exposure to iodocarb-treated metalworking fluids:

- A maximum concentration of iodocarb in metalworking fluid of 750 ppm.

Next steps

Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document. Comments on the proposed decision can be submitted during the consultation period to the PMRA through PMRA Publications, or the Public Engagement Portal (Public Engagement Forms - Consultation Comment). For more information or if you have questions, contact the PMRA's Pest Management Information Service.

Before making a special review decision on iodocarb under section 21 of the *Pest Control Products Act*, the comments received during the consultation period will be taken into consideration in preparation of the final special review decision document. A science-based approach will be applied in making a final decision on iodocarb. In accordance with subsection 28(5) of the *Pest Control Products Act*, Health Canada will then publish a final special review decision document, which will include the decision, the reasons for it, a summary of the comments received on the proposed special review decision during the consultation period, and Health Canada's response to these comments.

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 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.

Evaluation of the aspects of concern for the special review

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

To assess the aspects of concern, Health Canada considered the information that prompted the special review and other information currently available relevant to the aspects of concern, including the section 12 data submitted as a result of the previous re-evaluation decision for iodocarb (RVD2011-04) as well as the Re-evaluation of Antisapstain and Joinery Uses of Iodocarb (RVD2017-05).

1.0 Human health assessment

1.1 Potential changes to toxicology endpoints previously used for human health risk assessment

As part of the special review, Health Canada's Pest Management Regulatory Agency (PMRA) assessed available information to determine whether toxicology reference values previously used for the re-evaluation of iodocarb warranted revision.

Dermal toxicology reference values
Dermal toxicology reference values were recently updated for the re-evaluation of antisapstain and joinery uses of iodocarb (PRVD2016-25; RVD2017-05). These values were also used for the special review of iodocarb.

Inhalation toxicology reference values
Exposure to iodocarb from antisapstain and joinery uses is predominately by the dermal route; therefore, inhalation toxicology reference values were not established as part of that re-evaluation.

Since the re-evaluation initiation in 2010 (PRVD2010-05, RVD2011-04), three inhalation studies became available which are suitable for assessment of short- and intermediate term inhalation scenarios (Appendix II). The most relevant of these studies for risk assessment is the 13-week study which established a NOAEC of 0.23 mg/m^3 (equivalent to 0.06 mg/kg bw/day). The 5-day study established a similar NOAEC, while the 2-week study established a LOAEC of 4 mg/m^3, the lowest dose tested. Qualitatively the effects identified in these three studies were similar; however, with longer duration of exposure the effects increased in incidence and severity.

For the short- and intermediate-term inhalation scenarios, the 13-week study which established a NOAEC of 0.23 mg/m^3 (equivalent to 0.06 mg/kg bw/day) was selected for risk assessment. A target margin of exposure (MOE) of 100 was established, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The resulting reference value is 0.0023 mg/m^3 (equivalent to 0.0006 mg/kg bw/day). This reference value is protective of concerns identified for indirectly exposed unborn or nursing children (pregnant

women in the workplace) as discussed in PRVD2016-25, and it is more conservative than the reference values established in using the one generation reproductive toxicity study selected for the dermal toxicology reference value (NOAEL = 10 mg/kg bw/day, MOE = 300; resulting oral reference value = 0.03 mg/kg bw/day).

For the long-term inhalation exposure scenario, no long-term inhalation study is available. A route specific 13-week inhalation study, discussed above, is available. Of the available studies considered for long-term oral exposure scenarios, and potentially applicable to the long-term inhalation scenario risk assessment, the one generation gavage reproductive study was chosen. This study defines the lowest oral NOAEL value in the database and was used for establishing the ADI and for the long-term dermal exposure scenario risk assessment. However, the oral NOAEL value established is higher than the short- to intermediate-term inhalation NOAEC value. Since the observed toxicity via the inhalation route is expected to increase in severity with time, the 13-week inhalation toxicity study was chosen for the long-term inhalation exposure scenario risk assessment and a threefold uncertainty factor was applied for extrapolation from intermediate- to long-term exposure. The resulting reference value, 0.0008 mg/m^3 (equivalent to 0.0002 mg/kg bw/day) is considered protective of all populations.

1.2 Occupational exposure and risk assessment

Occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a 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.

1.2.1 Toxicology reference values

The toxicology reference values for occupational exposures are summarized in Appendix III.

For long-term dermal:
For long-term dermal exposure, the NOAEL of 10 mg/kg bw/day from the one-generation reproductive toxicity study in rats was selected for use in risk assessment. There were no suitable route specific dermal studies available. The target MOE is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The concerns outlined in the *Pest Control Products Act* hazard characterization Section in PRVD2016-25 regarding this endpoint are relevant to the worker population. For this reason, an additional threefold uncertainty factor was applied to this risk assessment to protect workers of child-bearing age.

Use of this NOAEL and target MOE of 300 provides a margin in excess of 600-fold to the LOAEL for thyroid effects in mouse and rat chronic toxicity studies and a margin in excess of 1600-fold to the NOAEL for hepatic tumours in male mice, thus addressing any tumorigenicity concerns. Refer to PRVD2016-25 for more information.

For long-term inhalation:
For long-term inhalation exposure, the NOAEC of 0.23 mg/m^3 (equivalent to 0.06 mg/kg bw/day) from the 13-week inhalation toxicity study in mice was selected for use in risk assessment. The target MOE is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. Since the observed toxicity via the inhalation route is expected to increase in severity with time, a threefold uncertainty factor was applied for extrapolation from intermediate- to long-term exposure.

Use of this NOAEL and target MOE of 300 provides a margin in excess of 100 000-fold to the LOAEL for thyroid effects in mouse and rat chronic toxicity studies and a margin in excess of 260 000-fold to the NOAEL for hepatic tumours in male mice, thus addressing any tumorigenicity concerns.

1.2.2 Dermal absorption

There is no dermal absorption data on file for iodocarb. As dermal exposure to metalworking fluids can cause irritation and contact dermatitis to machine operators, a dermal absorption value of 100% was selected for this special review. A value of 10% was previously used in the Re-evaluation Decision Document of iodocarb (RVD2011-04), based on the USEPA's 1997 Registration Eligibility Decision (RED). However, this value was based on acute toxicology data (apparent dermal absorption) and is not consistent with current policies for selection of dermal absorption values.

1.2.3 Occupational handler (mixer/loader) exposure and risk assessment

There are potential exposures to workers handling iodocarb commercial-class end-use products when treating metalworking fluids. Exposure to iodocarb is expected to be intermittent (a few minutes daily or once a week) over an intermediate to long-term duration (in other words, >30 days to a year).

Iodocarb end-use product labels do not specify open or closed system requirements; therefore, both types of systems were considered in the risk assessment:

- Manual transfer of liquids (conventional container)
- Closed transfer of liquids (assessed qualitatively)

Occupational risk to workers from open transfer activities in small scale facilities were assessed quantitatively. It was assumed that large scale facilities would have closed transfer systems already in place and these scenarios were assessed qualitatively.

A closed transfer (injection) system has the characteristics where there is no direct contact of workers with the active ingredient and thus workers are assumed to have no potential for exposure. Due to this, occupational risk for closed transfer (injection) systems were assessed qualitatively and risk were determined to be acceptable.

A manual transfer (open pour) of liquid scenario was considered for small scale metalworking fluid scenarios. No appropriate chemical-specific handler exposure data were available for

iodocarb. Therefore, dermal and inhalation exposures for occupational handlers were estimated using the liquid pour exposure study (PMRA# 2296582) submitted by the Antimicrobial Exposure Assessment Task Force II (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 this study were combined with the estimates of amounts of biocide applied per day by workers to treat metalworking fluids. There is limited information available to estimate the amount of iodocarb handled in one day in facilities where metalworking fluids are used. The USEPA "Antimicrobial Division Draft Summary of Amounts Handled or Treated for Occupational Handler Scenarios" (PMRA# 3084493) has standard values for the majority of industrial and material preservation scenarios. As facilities where metalworking fluids are used can come in a variety of sizes, an amount handled per day (AHPD) value of 19 L end-use product/day for occupational handlers based on the "Industrial Process and non-potable Water Systems" scenario was utilized to address all small scale facilities that would use an open pour method to mix, load, and apply the antimicrobial in metalworking fluids.

The calculated dermal and inhalation MOEs for workers handling iodocarb were below the target MOE and risks were not shown to be acceptable for workers wearing single layer personal protective equipment (PPE) (long pants, long-sleeved shirt, chemical-resistant gloves); as currently stated on the labels. Dermal risks could not be mitigated with additional PPE as exposure in the AEATF II study was primarily to the hands and exposure to the remainder of the body was minimal. To mitigate risks, it is proposed that the AHPD be restricted to 1.25 kg a.i./day/person, and facilities that use quantities above that are required to use a closed transfer system. The occupational handler (mixer/loader) risk assessment for iodocarb is presented in Appendix IV; Table 1.

1.2.4 Occupational secondary worker (machinist) exposure and risk assessment

There are potential exposures to secondary workers (machinists) from the use of treated metalworking fluids. Workers may be exposed to iodocarb over a long-term duration (in other words, >30 days to a year) via dermal contact of the treated metalworking fluids and through inhalation of the mist/aerosol containing iodocarb.

The dermal and inhalation exposure and risk assessments were conducted using the USEPA Chemical Screening Tool for Exposures & Environmental Release (ChemSTEER) systemic models and inputs.

Using the maximum registered concentration of 2000 ppm, dermal and inhalation MOEs were below the target MOE and risks were not shown to be acceptable. To mitigate risk, a lower registered concentration of 750 ppm will be proposed as the maximum concentration of iodocarb for use in metalworking fluids. At this concentration, dermal and inhalation risks were shown to be acceptable and it is within the currently registered label concentrations (2000 to 100 ppm). The exposure and risk assessment for secondary workers (machinists) exposed to metalworking fluids is presented in Appendix IV; Table 2.

1.3 Health incident reports

As of 5 September 2024, no incident reports involving iodocarb related to the aspects of concern had been reported to the PMRA.

List of abbreviations

µg	microgram
µm	micrometre
AEATF II	Antimicrobial Exposure Assessment Task Force II
a.i.	active ingredient
bwg	body weight gain
d	day(s)
DACO	Data code
DEA	dietary exposure assessment
DEEM	dietary exposure evaluation model
EDE	estimated daily exposure
fc	food consumption
kg	kilograms
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
L	litre
LOAEL	lowest observable adverse effect dose level [mg ai/kg bw]
LOC	level of concern
LOD	limit of detection
LOAEL	lowest observable adverse effect dose level [mg ai/kg bw]
m	metre
mg	milligram
mL	millilitre
MOE	margin of exposure
MWF	Metalworking fluid
No.	number
NOAEL	No Observed Adverse Effect Level
NOAEC	No Observed Adverse Effect Concentration
NOEC	No Observed Effect Concentration
Nss	Not statistically significant
OECD	Organisation for Economic Co-operation and Development
PCP	Pest control products
PCPA	*Pest Control Products Act*
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
RQ	risk quotient
ss	statistically significant
TSMP	Toxic Substance Management Policy
USEPA	United States Environmental Protection Agency
wt	weight

Appendix I Registered products containing Iodocarb used in metalworking fluids in Canada[1]

Table 1 Products containing iodocarb subject to proposed label amendments

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
21751	Commercial	Troy Chemical Corporation	Polyphase AF-1	Solution	40%
31675	Commercial	Troy Chemical Corporation	Polyphase P-20TEP	Solution	20%
30796	Commercial	Troy Chemical Corporation	Polyphase PW40	Suspension	40%
32569	Commercial	Thor GMBH	Thor Acticide IPS 20 Industrial Fungicide	Solution	20%
33784	Commercial	Thor GMBH	Acticide IPW 40	Suspension	40%
34217	Commercial	Lanxess Corporation	Preventol MP 400 D	Suspension	39.7%

[1] As of 10 September 2024, excluding discontinued products or products with a submission for discontinuation.

Appendix II Toxicity studies – Point of departure and endpoint

Table 1 Details of toxicity studies used for the special review of iodocarb

Study/Species/# of animals per group	Dose Levels/Purity of test material	NOAEL (mg/kg bw/day)	Results/Effects
5-d Inhalation Study Sprague Dawley Rats (whole body exposure) 5/sex/group PMRA No.1241709	Purity > 97% 0, 0.3, 1.0 or 3.9 mg/m^3 6hrs/d (5 exposures) Aerodynamic diameter <6µm ~70%	NOAEC = 0.3 mg/m^3	**≥ 1 mg/m^3**: Epithelial hyperplasia in the ventral region (minimal: 0, 0, 4, 3 and 0, 0, 5, 2 ♂/♀; moderate: 0, 0, 0, 1 and 0, 0, 0, 3 ♂/♀) and hyperplasia (0 ,0 ,2 ,1 and 0, 0, 1, 0 ♂/♀) or squamous metaplasia (0,0,2,3 and 0,0,0,4 ♂/♀) in the ventrolateral regions, with necrosis of the underlying cartilage (0, 0, 4, 5 and 0, 0, 3, 5 ♂/♀) @ 3.9 mg/m^3: ↓ nss bwg (♂)
2-wk Repeat Dose Inhalation Study Sprague Dawley Rats (whole body exposure) 5/sex/group PMRA No.1241710	Purity>97% 0, 4, 10, 38, or 67 mg/m^3 6hrs/day 5 days/wk (except MHD and HD groups with 3 exposures only) MMAD (µm): 1.97-2.51	LOAEC = 4 mg/m^3	**≥ 4 mg/m^3**: ↑ Epithelial hyperplasia in the ventral and ventro-lateral region of the larynx, squamous metaplasia in the ventrolateral region and necrosis of the underlying cartilage **≥ 10 mg/m^3**: agitated grooming of snout and eyes closed/half closed; noisy respiration, sneezing and brown staining around snout and jaws; ↓ ss bwg and overall water consumption (♂), ↓ fc; high incidences of gaseous distension and minimal contents of caecum (in decedent ♂, likely due to ↓fc); ↑ liver wt (♂) **≥ 38 mg/m^3**: mortality (1♀ on day 1); additional brown staining around forepaws, red ears, red limbs, discharges from snout/nostril; bw loss; ↑ incidences of lung congestion, and gaseous distension and minimal contents of gastrointestinal tract in decedent rats **@ 67 mg/m^3**: mortality (1♂ and ♀ each on day 2 and day 3); licking inside of mouth; gasping; rubbing chin on grid mesh floor
13-Week Inhalation Toxicity Study In Rat (whole body exposure) PMRA No.1241712	Purity >97% 0, 0.25, 1.25, 6.25 mg/m^3 0.25 mg/m^3 (repeat) Analysed: 0, 0.23 mg/m^3 (repeat),0.30, 1.16, 6.70, MMAD of 1.55 and 3.5µm (67.5–83.1% <6µm) MMAD of 1.55 and	NOAEC=0.23 mg/m^3	**0.3 mg/m^3:** ↑ epithelial hyperplasia and/or necrosis of the ventral cartilage (at termination) in larynx; ↓ mean corpuscular volume (non-adverse ♂); ↑ glutamic-pyruvic transaminase (GPT) levels (~11–18%, ♀) **≥ 1.16 mg/m^3:**↑ glucose (wk13 ♀); ↑ glutamic-pyruvic transaminase (GPT) levels (~26-39% wk 13, ♂); ↓ brain cholinesterase (wk14♀) **@ 6.70 mg/m^3 :** closed half-closed eyes during exposure, red ears; ♀); ↓ bw (-5%) and bwg (nss -10%) (♂); Epithelial hyperplasia (mostly moderate) in the ventral region, squamous metaplasia in the ventrolateral region

Study/Species/# of animals per group	Dose Levels/Purity of test material	NOAEL (mg/kg bw/day)	Results/Effects
	3.5µm (67.5–83.1% <6µm)		and necrosis of the ventral cartilage, epithelial hyperplasia over the arytenoid projections, epithelial ulceration in the ventral region and atrophy of the sub-mucosal glands in larynx; ↑ incidence of aggregates of macrophages (4/15, 3/13, 3/15, 7/15 in ♂ and 1/15, 2/13, 4/15 5/15 in ♀); ↓ plasma cholinesterase (-22-36% wk 2, 13)↓ brain cholinesterase (-18%, wk 13) (♂); ↑ packed cell volume and RBCs, ↓ mean corpuscular haemoglobin concentration and reticulocyte numbers, erythrocyte cholinesterase (wk 2) and ↑ albumin (wk 13) (not adverse, ♀) Brain cholinesterase (µmol/g/min, terminal) ♂: 5.77, 5.02, 5.05, 4.80* (-17%) ♀: 6.59, 6.38, 4.97*(-24%), 4.87*(-26%)
One generation Reproductive (oral-gavage) study Crl : CD(SD)BR VAF Rats 25/sex/dose PMRA No.1241720	Purity >97% F0 mated 0, 10, 30 or 100 mg/kg bw/day in 1% aqueous methylcellulose F1 25/sex/group 0, 10, 30 or 100mg/kg bw/day in 1% aqueous methylcellulose PND25-13wks old (mated) 15/sex/group untreated F2a Mated within groups till GD13, but weaned till PND21	Maternal NOAEL = 10 mg/kg bw/day Reproductive NOAEL=10 mg/kg bw/day Offspring NOAEL = 10 mg/kg bw/day	Maternal ≥ 10 mg/kg bw/day: mortality (1F1 undetermined); ↓ abs and rel F1 lung (-7-9%/-9% ♂/♀), adrenal gland (-5-10%/-15% ♂/♀) and kidneys (-8-11%/-8% ♂/♀) wt ; ↓ heart (rel ss)(-9%-12% F1♂) ≥ 30 mg/kg bw/day: ↑ sacrifice 2F1♀ with multiple clinical signs including piloerection, emaciation, unsteady gait etc); elongated/difficult parturition (1 F0, 4F0); ↑ salivation, hunched posture and paddling with both forepaws (were not considered treatment-related); ↓fc (F1 ♂ wks 1 and 14); ↑ incidence of thickened stomach lining (F1 ♀); ↓ liver wt (F0♀ -7%, -10%); ↓ pup survival (F1) and ↑ abs/rel ovary wt (F0: 9%, 10% and 16%/22); ↓ F1 heart wt (-7% ♀); retardation of pup growth (F1 and 2) and pup development (F2). @ 100 mg/kg bw/day: ↑ sacrifice (4 HD F0♀ elongated parturition, non-treatment related); ↓bw (-6% F0 and F1♂) and bwg (F0♂:-20-40% during days 1-8, 64-71, 99-106, F0♀:-28-39% premating days 50-64, 1st week lactation ♀) and fc (F0:-8% 1st wk treatment ♂; - 19%-23% PND 1-7, 7-14♀); ↑ abs and rel liver wt (F0:8% nss,/ 17%ss ♂); ↑ rel epididymides (F0:13%), testes (F0: 10%) Reproductive ≥ 30 mg/kg bw/day: ↑ ovary weights @ 100 mg/kg bw/day: ↓ copulation index (-20% F0); ↓ fertility indices (-20% and -25% F0, F1 respectively) and an increase in the number of females that were sacrificed during parturition. Offspring

Study/Species/# of animals per group	Dose Levels/Purity of test material	NOAEL (mg/kg bw/day)	Results/Effects
			≥ 30 mg/kg bw/day: ↑ no. of pups sacrificed prematurely/found dead; ↓ mean live birth index (F0:98%, 98, 90, 79.5%); ↓ pup survival (F1:88%, 94%, 67%, 28%); retardation of pup growth (F1&2) and pup development (F2); ↓ bw F2 (-5%/-9% ♂/♀); ↓ no. of F2 pups with eyes open on PND 15 (-13%) @ 100 mg/kg bw/day: ↓ pup survival and retardation of pup growth and development; ↓ bw (F1 -14% throughout PND 0-21) **Sensitivity of the young**

Appendix III Toxicology reference values for health risk assessment

Table 1 Toxicology reference values for use in health risk assessment for iodocarb

Exposure scenario	Study	Point of departure and endpoint	Target MOE
Dermal – all durations [a]	1-generation reproduction study	NOAEL of 10 mg/kg bw/day Based on decreased pup survival and developmental retardation in the presence of maternal toxicity	300 (PCPA factor of threefold)
Short-, and intermediate-term inhalation	13-week inhalation study in rats	NOAEC = 0.23 mg/m^3 (equivalent to 0.06 mg/kg bw/day) Based on increased epithelial hyperplasia and/or necrosis of the ventral cartilage in larynx and enzyme levels	100
Long-term inhalation			300 (threefold UF for IT to LT extrapolation)
Cancer	Not required		

MOE = margin of exposure; NOAEL = no observed adverse effect level; NOAEC = no observed adverse effect concentration; UF = uncertainty factor; IT = intermediate-term; LT = long-term; PCPA = *Pest Control Products Act*

[a] Toxicology reference values from the Proposed Re-evaluation Decision Document of Antisapstain and Joinery Uses of Iodocarb (PRVD2016-25).

Appendix IV Occupational exposure and risk assessment

Table 1 Iodocarb long-term occupational handler (mixer/loader) exposure and risk assessment

Scenario	AHPD[a]		Dermal exposure[b] (mg/kg bw/day)	Inhalation exposure[c] (mg/kg bw/day)	Dermal MOE[d]	Inhalation MOE[e]
	L EP/day	kg a.i./day[f]			Target MOE =300	
Manual Open Pour; Applicator PPE: Single layer (long-sleeved shirt, long pants) + CR gloves						
Metalworking Fluid	19	19.7[g]	0.525	0.00125	**19**	**48**
		9.84[h]	0.263	0.000627	**38**	**96**
	2[g]–5[h]	1.25	0.033	0.000079	300	756

PPE = personal protection equipment; CR = chemical-resistant; AHPD = amount handled per day; a.i. = active ingredient; MOE = margin of exposure; NOAEL = no observed adverse effect level; NOAEC = no observed adverse effect concentration; UE = unit exposure; BW = body weight; L EP = litres of end-use product

Bolded cells indicate MOEs less than the target MOE and risks are not shown to be acceptable.

[a] AHPD values (L EP/day) based on USEPA (2018). These were converted into kg active ingredient using the % concentration of iodocarb and density.

[b] Dermal Exposure (mg/kg bw/day) = AHPD (kg a.i./day) × UE (2135 µg/kg a.i.) × Dermal Absorption (100%) × 0.001 (µg to mg) / BW (80 kg).

[c] Inhalation Exposure (mg/kg bw/day) = AHPD (kg a.i./day) × UE (5 µg/kg a.i.) × 0.001 (µg to mg) / BW (80 kg).

[d] MOE = NOAEL (mg/kg bw/day) / Exposure (mg/kg bw/day). Based on a NOAEL of 10 mg/kg bw/day from a 1-generation reproduction study. Target MOE of 300 for all exposure durations.

[e] MOE = NOAEC (mg/kg bw/day) / Exposure (mg/kg bw/day). Based on a NOAEC of 0.06 mg/kg bw/day from a 13-week inhalation study in rats. Target MOE of 300 for long-term exposure durations.

[f] kg a.i./day = AHPD (L EP/day) × EP Concentration (%) × EP Density (kg/L)

[g] Calculated based on the AHPD (kg ai/day) where MOEs ≥ target MOE using maximum concentration in registered EP (40%) and maximum EP density (1.3 kg/L).

[h] Calculated based on the AHPD (kg ai/day) where MOEs ≥ target MOE using minimum concentration in registered EP (20%) and maximum EP density (1.3 kg/L).

Table 2 Iodocarb long-term exposure and risk assessment for secondary workers (machinists) exposed to metalworking fluids

Scenario	Concentration		Dermal exposure[a] (mg/kg bw/day)	Inhalation exposure[b] (mg/kg bw/day)	Dermal MOE[c]	Inhalation MOE[d]
	ppm	% a.i.			Target MOE = 300	
Metalworking Fluid	2000 (max rate)	0.2	0.0888	0.000250	**113**	**240**
	100 (min rate)	0.01	0.00444	0.000125	2252	4800
	750	0.075[e]	0.0333	0.0000938	300	640

MOE = margin of exposure; a.i. = active ingredient; BW = body weight; WF = weight fraction of chemical in MWF; rate = concentration of a.i. in MWF; ppm = parts per million; max = maximum; min = minimum

Bolded cells indicate MOEs less than the target MOE and risks are not shown to be acceptable.

[a] Dermal Exposure (mg/kg bw/day) = Surface area of both hands and forearms (2030 cm^2) × WF (% a.i.) x Retention Quantity of MWF on skin (1.75 mg/cm^2) × Frequency of Events (1 event/day) / BW (80 kg)

[b] Inhalation Exposure (mg/kg bw/day) = MWF air concentration (1 mg/m^3) × WF (% a.i.) × Inhalation Rate (1.25 m^3/hr) × Exposure Duration (8 hours/day) / BW (80 kg)

[c] MOE = NOAEL (mg/kg bw/day)/Exposure (mg/kg bw/day). Based on a NOAEL of 10 mg/kg bw/day from a 1-generation reproduction study. Target MOE of 300 for all exposure durations.

[d] MOE = NOAEC (mg/kg bw/day)/Exposure (mg/kg bw/day). Based on a NOAEC of 0.06 mg/kg bw/day from a 13-week inhalation study in rats. Target MOE of 300 for long-term exposure durations.

[e] Iodocarb concentration where both dermal and inhalation MOEs reach the target MOE and risks were shown to be acceptable.

Appendix V Proposed label amendments for products containing Iodocarb used in metalworking fluids

The proposed label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements below.

1.0 Label amendments relating to the health risk assessment

1.1 Use directions

Metalworking fluids

The following information is to be placed in a separate box on the label titled "For Metalworking Fluid" that is specific for metalworking fluids.

When handling iodocarb end-use products for metalworking use, the following statements are proposed:

- "When manually transferring (open pouring) products to treat metalworking fluids, DO NOT handle more than [*1.25 kg a.i to be reported in product equivalent value*] per person, per day. " *As indicated by square brackets, the amount of iodocarb in the statement (i.e., 1.25 kg ai) is to be converted into the corresponding amount of product by the registrant for each product label.*

- "If handling more than [*1.25 kg a.i to be reported in product equivalent value*] per person per day, use a closed loading and transfer system only (i.e., dry coupling)." *As indicated by square brackets, the amount of iodocarb in the statement (i.e., 1.25 kg ai) is to be converted into the corresponding amount of product by the registrant for each product label.*

  "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."

For products with metalworking fluid uses, it is proposed that the maximum concentration of iodocarb in metalworking fluids is reduced from 2000 ppm to 750 ppm.

The following statement is proposed:

- "**DO NOT** apply iodocarb in metalworking fluids at concentrations higher than [*750 ppm to be reported in product equivalent value*]." *As indicated by square brackets, the amount of iodocarb in the statement (i.e., 750 ppm) is to be converted into the corresponding amount of product by the registrant for each product label.*

References

A. Information Considered in the Human Health Risk Assessment

Documents submitted by the registrant

PMRA Document Number	Reference
2348175	2013, Post-application: Passive Dosimetry in Metalworking Fluids. DACO: 5.6(A)
2348174	2013, Iodocarb Use Description/Scenario in Metalworking Fluids, DACO: 5.2
1241709	1994, Omacide IPBC 5-day Repeat Dose Inhalation Toxicity Study in Rats. DACO: 4.2.3,4.2.9
1241710	1994, Omacide IPBC 2-Week Repeat Dose Inhalation Toxicity Study in Rats. DACO: 4.2.3,4.2.9
1241712	1994, Omacide IPBC 13-Week Inhalation Toxicity Study in Rats. DACO: 4.3.6
1241720	1996, Oral Gavage Rat One Generation Reproductive Toxicity Study (Expanded to Two Generation). DACO: 4.5.1

List of Task Force Studies/Information

PMRA Document Number	Reference
2296582	2012, A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of a Liquid Containing an Antimicrobial. DACO: 5.4

Additional Information Considered

Published Information

PMRA Document Number	Reference
	PMRA, 2011. RVD2011-04. Iodocarb. Re-evaluation Decision Document. March 10, 2011.
	PMRA, 2016. PRVD2016-25. Antisapstain and Joinery Uses of Iodocarb. Proposed Re-evaluation Decision. December 30, 2016.
	PMRA, 2017. Antisapstain and Joinery Uses of Iodocarb. RVD2017-05. Re-evaluation Decision. October 13, 2017.

Unpublished Information

PMRA Document Number	Reference
3084493	2018. USEPA. Summary of Amounts Handled or Treated for Occupational Handler Scenario. November 28, 2018. Draft. DACO: 5.2
2737108	1996. Data Evaluation Record - Subchronic Inhalation Toxicity - Rat, Kenny, T.J. (1994) Omacide IPBC. 13-Week Inhalation Toxicity Study in Rats. Huntington Research Center Ltd., Huntington, Cambridgeshire, PE18 6ES, England. Laboratory Project Number TXC 7/942772. November 3, 1994, MRID 43530203. DACO: 4.3.6