Proposed Registration Decision PRD2011-10

Icaridin

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Overview

Proposed Registration Decision for Icaridin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Icaridin Technical Insect Repellent, All-Family Insect Repellent Spray, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray I, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray II, OFF! Active Insect Repellent Clean Feel, OFF! Family Care Clean Feel Insect Repellent Towelettes and OFF! Deep Woods Pump Spray Insect Repellent Clean Feel, containing the technical grade active ingredient icaridin, as a personal insect repellent against mosquitoes and various pests as indicated on the label.

An evaluation of available scientific information found that, under the approved conditions of use, these products have value and do not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation sections provide detailed technical information on the human health and value assessments of icaridin and All-Family Insect Repellent Spray, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray I, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray II, OFF! Active Insect Repellent Clean Feel, OFF! Family Care Clean Feel Insect Repellent Towelettes and OFF! Deep Woods Pump Spray Insect Repellent Clean Feel.

What Does Health Canada Consider When Making a Registration Decision?

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

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

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

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on icaridin, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on icaridin, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

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

What Is Icaridin?

Icaridin is the active ingredient contained in All-Family Insect Repellent Spray, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent I, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent II, OFF! Active Insect Repellent Clean Feel, OFF! Deep Woods Pump Spray Insect Repellent Clean Feel and OFF! Family Care Clean Feel Insect Repellent Towelettes. It is a personal insect repellent for application on human skin. Its mode of action is not fully understood. One hypothesis is that icaridin affects arthropod olfactory neurons, resulting in their inability to detect host attractants. Another is that the repellent evaporates from the skin into the air, forming a layer of scent that camouflages the attractants (carbon dioxide and lactate) emitted by the human host, and therefore the arthropod cannot find the host.

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

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

Health Considerations

Can Approved Uses of Icaridin Affect Human Health?

Products containing icaridin are unlikely to affect your health when used according to label directions.

Exposure to icaridin will occur through the application of insect repellent products containing this active ingredient to human skin. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

In laboratory animals, technical grade active ingredient icaridin was of low acute toxicity by the oral, dermal and inhalation routes of exposure. It was moderately irritating to the eyes of rabbits, and as such the hazard statement "Warning Eye Irritant" is required on the label. Icaridin was not irritating to the skin and did not cause an allergic skin reaction.

All of the end-use repellent products containing icaridin were of low acute toxicity via the oral, dermal, and inhalation routes of exposure. None of the products were irritating to the skin and none caused an allergic skin reaction. All products were moderately irritating to the eyes, and consequently the hazard statement "Warning- Eye Irritant" is required on the product labels.

Health effects in animals given repeated doses of icaridin included effects on the liver and kidney. Icaridin did not cause cancer in animals and did not damage genetic material. There was no indication that icaridin caused damage to the nervous system or immune system.

Icaridin did not have an effect on the ability to reproduce. When icaridin was given to pregnant or nursing animals, no effects on the developing fetus or juvenile animal were observed, indicating that the young do not appear to be more sensitive to icaridin than the adult animal.

The risk assessment protects against the effects of icaridin by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Risks in Residential and Other Non-Occupational Environments

Residential and other non-occupational bystander risks are not of concern when All-Family Insect Repellent Spray, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray I and II, OFF! Active Insect Repellent Clean Feel, OFF! Deep Woods Pump Spray Insect Repellent Clean Feel, and OFF! Family Care Clean Feel Insect Repellent Towelettes are used according to label directions.

People who apply the products to themselves as well as people who have the products applied to them, come in direct contact with icaridin residues on the skin. Therefore, the domestic uses of the 10% and 20% icaridin pump spray, the 10% icaridin aerosol and the 20% icaridin towelettes as personal insect repellents are considered acceptable for adults, youth, children, toddlers and infants (> 6 months).

Taking into consideration the product specific application rates, the number of applications, the protection time and the exposure duration, it was determined that the risks to these individuals are not a concern.

For bystanders, exposure was not quantified, as it is expected to be minimal in comparison to the exposure to users. Therefore, health risks to bystanders are not of concern.

Occupational Risks From Handling All-Family Insect Repellent Spray, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray I and II, OFF! Active Insect Repellent Clean Feel, OFF! Deep Woods Pump Spray Insect Repellent Clean Feel, and OFF! Family Care Clean Feel Insect Repellent Towelettes

Occupational risks from handling the icaridin products were not quantified, as it is expected that workers will not use these products in greater quantities than residential users. Therefore, health risks to workers are addressed by those of residential users.

Value Considerations

What Is the Value of All-Family Insect Repellent Spray, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent I, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent II, OFF! Active Insect Repellent Clean Feel, OFF! Deep Woods Pump Spray Insect Repellent Clean Feel and OFF! Family Care Clean Feel Insect Repellent Towelettes?

These end-use products repel mosquitoes, ticks and black flies, which are important blood-feeding pest arthropods.

Sufficient efficacy data were provided to support the following uses:

- All-Family Insect Repellent Spray (containing 20% icaridin) for seven hours of protection from mosquitoes and eight hours of protection from ticks. Use of these products to provide eight hours of protection from black flies was conditionally supported.

- Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent I and Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent II (containing 10% icaridin) for five hours of protection from mosquitoes. Use of these products to provide seven hours of protection from ticks was conditionally supported.

- OFF! Active Insect Repellent Clean Feel (containing 10% icaridin) for five hours of protection from mosquitoes.

- OFF! Deep Woods Pump Spray Insect Repellent Clean Feel and OFF! Family Care Clean Feel Insect Repellent Towelettes (containing 20% icaridin) for seven hours of protection from mosquitoes and eight hours of protection from ticks.

Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label of All-Family Insect Repellent Spray, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray I, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray II, OFF! Active Insect Repellent Clean Feel, OFF! Family Care Clean Feel Insect Repellent Towelettes and OFF! Deep Woods Pump Spray Insect Repellent Clean Feel, to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

A risk assessment was not performed for infants under six months of age since it is assumed that non-chemical measures can be utilized to protect this population from biting pressures. Therefore, all products carry the statement: “Do not use on infants under 6 months of age”.

Next Steps

Before making a final registration decision on icaridin, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency’s response to these comments.

Other Information

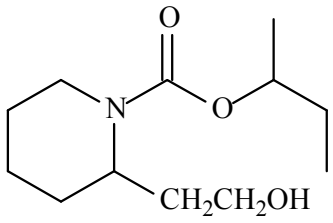
When the PMRA makes its registration decision, it will publish a Registration Decision on icaridin (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA’s Reading Room (located in Ottawa).

Science Evaluation

Icaridin

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Icaridin
Function	Insect repellent
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(RS)-*sec*-butyl (RS)-2-(2-hydroxyethyl)piperidine-1-carboxylate
2. Chemical Abstracts Service (CAS)	1-piperidinecarboxylic acid, 2-(2-hydroxylethyl)-, 1-methylpropyl ester
CAS number	119515-38-7
Molecular formula	$C_{12}H_{23}NO_3$
Molecular weight	229.32
Structural formula	
Purity of the active ingredient	98.7%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Icaridin Technical

Property	Result
Colour and physical state	Colourless liquid
Odour	Odourless
Melting range	<-170°C
Boiling point	296°C
Density at 20°C	1.07 g/mL
Vapour pressure at 20°C	3.4×10^{-2} Pa at 20°C 5.9×10^{-2} Pa at 25°C
Ultraviolet (UV)-visible spectrum	pH / λ_{max} (nm) / ε (cm^{-1} mol^{-1} L) 4 / 198 / 3.44×10^3 7 / 204 / 1.91×10^3 9 / 207 / 3.44×10^3
Solubility in water at 20°C	8.2 g/L (pH 4-9) 8.6 g/L (unbuffered water)
Solubility in organic solvents at 20°C	Solvent / Solubility (g/L) n-heptane >250 xylene >250 dichloromethane >250 2-propanol >250 1-octanol >250 polyethlene glycol >250 acetone >250 ethylacetate >250 acetonitrile >250 dimethylsulfoxide >250
n-Octanol-water partition coefficient (K_{ow})	pH / log Kow 4-9 / 2.23 unbuffered / 2.11
Dissociation constant (pK_a)	N/A
Stability (temperature, metal)	Stable up to 160°C

End-Use Product—All-Family Insect Repellent Spray

Property	Result
Colour	Colourless
Odour	Perfumed odour – it is assumed that the alternate formulation of this end-use product without fragrance would have no odour.
Physical state	Liquid
Formulation type	SN (solution)
Guarantee	20%
Container material and description	10 mL – 1L plastic bottle
Density	0.977-0.987 g/mL
pH of 1% dispersion in water	7-9
Oxidizing or reducing action	The product does not contain any oxidizing or reducing agents.
Storage stability	Stable in HDPE under commercial storage conditions (25˚C, 60% RH) for one year
Corrosion characteristics	No corrosion to HDPE bottle was observed in 12 months.
Explodability	Not explosive

End-Use Product—OFF! Deep Woods Pump Spray Insect Repellent Clean Feel

Property	Result
Colour	Colourless
Odour	Characteristic alcohol
Physical state	Liquid
Formulation type	SN (solution)
Guarantee	20%
Container material and description	50-350 mL plastic bottle
Density	0.95 g/mL

Property	Result
pH of 1% dispersion in water	5.6
Oxidizing or reducing action	The product is neither an oxidizing nor a reducing agent.
Storage stability	Stable for one year stored in plastic containers at ambient temperature
Corrosion characteristics	No corrosion to plastic containers was observed during one year storage at ambient temperature.
Explodability	Not expected to be explosive based on the chemical nature of the formulation ingredients.

End-Use Product—OFF! Active Insect Repellent Clean Feel

Property	Result
Colour	N/A
Odour	N/A
Physical state	Liquid
Formulation type	PP (pressurized product)
Guarantee	10%
Container material and description	Metal, 100-500 g
Density at 20°C	0.85 g/mL
pH of 1% dispersion in water	8.5
Oxidizing or reducing action	The product is neither an oxidizing nor a reducing agent.
Storage stability	Stable for one year commercial storage
Corrosion characteristics	No corrosion to the metal can was observed during one year storage.
Explodability	Not expected to be explosive based on the chemical nature of the formulation ingredients. However, like all pressurized products, the label bears the explosive precautionary symbol.

End-Use Product—Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray I

Property	Result
Colour	Water white to straw coloured
Odour	Fragrance
Physical state	Liquid
Formulation type	PP (pressurized product)
Guarantee	10.0%
Container material and description	Aerosol package is a monobloc aluminum metal with PAM (polyamideimide) 8460 internal lining and the aerosol valve is Seaquist VX-86 aluminum mounting cup with an epoxy lining.
Specific gravity at 25°C	0.87-0.93 (without propellant)
pH of 1% dispersion in water	7.5-8.5 at 25°C (without propellant)
Oxidizing or reducing action	The product is neither an oxidizing nor a reducing agent.
Storage stability	Stable for one year at ambient temperature in the commercial package
Corrosion characteristics	No corrosion to the packaging material was observed during one year storage.
Explodability	Not explosive (formulation only) The label has a Caution - explosive symbol because it is a pressurized product.

End-Use Product—Avon Skin So Soft SSS Bug Guard Plus Insect Repellent Spray II

Property	Result
Colour	Hazy water white
Odour	Fragrance
Physical state	Liquid
Formulation type	SN (solution)
Guarantee	10.0%

Property	Result
Container material and description	HDPE bottles
Specific gravity at 25°C	0.87-0.93
pH	6.75-7.75 at 25°C (10% in demineralised water)
Oxidizing or reducing action	The product does not contain any oxidizing or reducing agents.
Storage stability	Stable for one year at ambient temperature in the commercial package
Corrosion characteristics	No corrosion to the HDPE container was observed during 56 days of storage.
Explodability	The product does not contain explosive components.

End-Use Product—OFF! Family Care Clean Feel Insect Repellent Towelettes

Property	Result
Colour	White
Odour	Alcoholic odour
Physical state	Liquid
Formulation type	IF (impregnated fabric) for the towelette
Guarantee	20%
Container material and description	HDPE bottles
Density at 20°C	0.95 g/mL
pH	5.6
Oxidizing or reducing action	The product is neither an oxidizing nor a reducing agent.
Storage stability	The product is stable over 12 month storage at room temperature.
Corrosion characteristics	The product was shown not to be corrosive over 12 months at room temperature.
Explodability	Not expected to be explosive based on the chemical nature of the formulation ingredients.

1.3 Directions for Use

All-Family Insect Repellent Spray
Hold 15 to 20 cm from skin while spraying, keeping nozzle pointed away from face. Slightly moisten skin with a slow sweeping motion. Apply on face by first spraying small amounts in palms of hands and spreading on face and neck. Apply sparingly around ears, do not apply under clothing. Reapply if necessary every seven hours for protection from mosquitoes and eight hours for protection from ticks. Do not apply more than two times a day.

Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray I
Hold container 15 to 20 cm from skin or clothing and spray with a slow sweeping motion liberally and evenly.
TO APPLY TO FACE: Spray palm of hand and rub on, avoiding the eye and lip area. Use just enough repellent to cover exposed skin.
FOR CONTINUED PROTECTION from mosquitoes reapply if necessary after five hours and for ticks reapply if necessary after seven hours. Do not exceed four applications per day.

Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray II
Hold container 15 to 20 cm from skin or clothing and spray liberally and evenly.
TO APPLY TO FACE: Spray palm of hand and rub on, avoiding the eye and lip area.
FOR CONTINUED PROTECTION from mosquitoes reapply if necessary after five hours and for ticks reapply after if necessary seven hours. Do not exceed four applications per day.

OFF! Active Insect Repellent Clean Feel
Apply sparingly and only when necessary. Reapply after five hours if necessary. TO APPLY TO FACE: Spray hand and apply sparingly avoiding eyes and mouth. Do not spray in enclosed spaces. Do not use under clothing.

OFF! Deep Woods Pump Spray Insect Repellent Clean Feel
Apply sparingly and only when necessary. Reapply after seven hours if necessary for protection from mosquitoes and eight hours if necessary for protection from ticks. TO APPLY TO FACE: Spray hand and apply sparingly avoiding eyes and mouth. Do not spray in enclosed spaces. Do not use under clothing.

OFF! Family Care Clean Feel Insect Repellent Towelettes
Unfold towelette and apply evenly over all exposed skin except eyes and mouth. Apply sparingly, not under clothing and only when necessary. Reapply after seven hours if necessary for protection from mosquitoes and eight hours if necessary for protection from ticks.

1.4 Mode of Action

The mode of action of icaridin is not fully understood. One hypothesis is that icaridin affects arthropod olfactory neurons, resulting in their inability to detect host attractants. Another is that the repellent evaporates from the skin into the air, forming a layer of scent that camouflages the attractants (carbon dioxide and lactate) emitted by the human host, and therefore the arthropod cannot find the host.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Icaridin Technical Insect Repellent have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for Icaridin Technical Insect Repellent (icaridin) was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to icaridin. The majority of studies were conducted via the dermal route of exposure, which is the most relevant route based on the use pattern (personal insect repellent). In order to prevent ingestion of the test material from the application site, test animals were fitted with Elizabethan collars (or rodent jackets in the case of the acute neurotoxicity study) in the majority of the studies. In addition, a series of studies were conducted to investigate the impact of the use of the rodent jackets on the interpretation of the study results. Three dietary studies in rats were also conducted.

Dermal toxicokinetic studies conducted with radiolabelled icaridin in rats showed that dermal absorption was rapid, and was similar between sexes following either single- or repeated-low dose administration. Absorption following a single high dose application was slightly lower than that which was observed following application of a single low dose. Maximum plasma concentrations were reached within 6-8 hours of dosing and were higher in females than in males. Evaporation of the test material was thought to account for approximately 18-23% of the applied dermal dose over the seven-day exposure period. Elimination occurred primarily via the urine, and was essentially complete within 48 hours. A slightly higher proportion of the administered radioactivity was eliminated in the urine of females as compared to males.

The highest residues of icaridin were found in the skin at the application site. Residues in the body were < 1% of the administered dose. Generally, the pattern of distribution of radioactivity among tissues was similar between the sexes and dose groups. The exception was the liver, in which levels of radioactivity in males were approximately 1.4- to 3.2-fold greater than those in females. Aside from the skin at the application site, the highest residue levels were found in the skin, fat, liver, kidneys and lungs.

Biotransformation of icaridin in the rat mainly involved phase I reactions resulting in metabolites hydroxylated in the piperidine ring and in the 2-methylpropyl ester side chain, and those with the alcohol group oxidised to a carboxyl group. Including parent compound, 18 metabolites were identified in the urine and feces of animals of both sexes. The overall metabolite profile was similar between sexes as well as between single and repeated dosing regimes. The major metabolites were isomers of 2-(2-acetyl)-1-piperidinecarboxylic acid esterified with 1-methyl-2-hydroxypropyl alcohol, 1-hydroxymethylpropyl alcohol, or 1-methylpropyl alcohol.

Icaridin was of low acute toxicity via the oral, dermal, and inhalation routes in rats. It was moderately irritating to the eyes of rabbits but not irritating to the skin. Icaridin was not a skin sensitizer when tested in guinea pigs.

All of the associated end-use products containing icaridin were of low acute toxicity via the oral, dermal, and inhalation routes of exposure. None of the products were irritating to the skin of rabbits, and none were dermal sensitizers when tested in guinea pigs. All of the end-use products were moderately irritating to the eyes.

Repeat-dose dietary studies conducted in rats revealed the liver and kidney to be the main target organs of toxicity following oral administration of icaridin, with decreases in body weight also observed. Increased liver weight and associated hepatocellular hypertrophy were observed in all studies but were considered an adaptive response due to the absence of any corroborating adverse liver findings. Increased kidney weight and an increased incidence of protein droplet degenerative nephropathy in males were noted at doses exceeding the limit dose. There was an indication of increased toxicity with increasing study duration when the results of the 28-day study were compared to those of the 14-day study. However, when the study was carried out over a slightly longer duration of 90 days, there was no indication of such an effect.

Repeat-dose dermal studies were conducted in rats, mice and dogs. The majority of the repeated dermal dosing studies utilized 200 mg/kg bw/day as the highest dose tested due to reported problems with the liquid test article spreading beyond the application site. Adverse effects were not observed at this dose level, and as such LOAELs were not established for most of the studies. Dermal irritation was observed in some of the studies, but was generally not dose-related and was attributed to an adaptive response of the skin resulting from prolonged, cumulative exposure to the test article.

The only repeat-dose dermal study with notable toxicity was the 90-day dermal study in rats in which adverse effects were observed at doses ≥500 mg/kg bw/day. Significant spreading of the test material occurred at the doses at which effects were observed, and oral ingestion of the test material through grooming behaviour could not be dismissed. The effects noted in this study were similar to those noted in the oral studies. Increased liver and kidney weights were reported, with associated histopathology in both organs, including liver hypertrophy, individual necrotic liver cells, slight hyaline degeneration in the kidney tubules, chronic inflammation of the kidneys and an increased incidence of foci of tubular regeneration. Kidney effects were seen only in males, as with the dietary studies. At the end of a 4-week recovery period, there was no indication of adverse effects in treated animals.

There were no treatment-related neoplastic lesions or non-neoplastic effects in rats or mice following chronic exposure to icaridin. Icaridin was not genotoxic based on the results from a battery of in vitro and in vivo tests assessing gene mutation, chromosomal aberration, unscheduled DNA synthesis, and micronucleus anomalies.

There was no evidence of neurotoxicity in dermal acute and subchronic neurotoxicity studies conducted in rats, nor was there any indication of neurotoxic potential for icaridin in the rest of the database. Dermal reproductive and developmental toxicity studies revealed no adverse effects on reproduction or fetal development.

Results of the toxicology studies conducted on laboratory animals with Icaridin Technical Insecticide and its associated end-use products are summarized in Tables 1a to e and 2 of Appendix I. The toxicology endpoints for use in the human health risk assessment are summarized in Table 3 of Appendix I.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found at the PMRA website. Incidents from Canada and the United States were searched and reviewed for icaridin. There are no incidents related to icaridin in the PMRA incident reporting database. Based on the limited information available from incidents reported in other countries, no serious health concerns were identified.

3.1.1 PCPA Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for Icaridin Technical Insect Repellent. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive and prenatal developmental toxicity studies. On the basis of this information, the PCPA factor was reduced to 1-fold.

3.2 Determination of Acute Reference Dose

An acute reference dose was not established since there are no proposed food uses.

3.3 Determination of Acceptable Daily Intake

An acceptable daily intake was not established since there are no proposed food uses.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Acute dermal exposure
An acute dermal endpoint was not established since there were no effects in the toxicology database that could be attributed to a single dose.

Short- to Intermediate-term dermal exposure (all populations)
The Canadian biting pest season is considered to take place between May and August (approximately four months); therefore, a short- to intermediate-term toxicology endpoint was considered appropriate for the risk assessment. Exposure is expected to occur mainly via the dermal route.

Due to the nature of the test material (liquid), the highest dose level tested in the dermal studies was limited by the amount of test material which could be applied to the animals without significant spreading/run-OFF. Results of toxicology testing indicated that the liver and kidneys were target organs of toxicity following repeated dietary and dermal dosing. In the 90-day dermal study, these effects were noted only at dose levels ≥500 mg/kg bw/day, levels at which significant spreading of the test material was reported, and oral ingestion of the test material through grooming behaviour could not be discounted.

The most appropriate study for this use scenario would be the 90-day dermal study in rats. However, due to dosing limitations in the dermal studies and the potential for oral ingestion at the effect levels in the 90-day dermal study, the NOAEL of 301 mg/kg bw/day from the 90-day dietary study in rats was considered the most appropriate endpoint for risk assessment purposes.

The target Margin of Exposure (MOE) selected for this endpoint is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variation. As outlined in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. This MOE is considered to be protective of adults, youth, children over the age of six months, and the unborn children of exposed women.

Incidental oral exposure (toddlers)
The oral route was also considered for toddlers due to the potential for hand-to-mouth incidental oral exposure. Since the dermal and oral routes of exposure are expected to co-occur in toddlers, these exposures were aggregated using the same intermediate-term endpoint discussed above.

3.4.1.1 Dermal Absorption

Two dermal absorption studies were submitted by the registrant; a human *in vivo* study and a rat *in vivo* study. The human study involved dermal application of both neat and 15% active ingredient in ethanol test materials at the same dose level, whereas the rat study involved only neat applications at three dose levels.

The human study was selected by the PMRA as the most relevant study to characterize dermal absorption as the end-use products are for use on humans and the products are co-formulated with ethanol. Further to this, the study was subject to oversight from an independent review board (IRB). The IRB used the Helsinki Declaration as the basis for their ethical evaluation and confirmed that the study volunteers provided informed consent prior to the start of the study; a copy of the IRB report and consent form was provided.

In light of the above, a dermal absorption value of 4% from the human dermal absorption study was considered appropriate for risk assessment purposes.

3.4.2 Residential Exposure and Risk Assessment

The current US EPA Residential Exposure Assessment Standard Operating Procedures (EPA 1997, updated 2001) do not include guidance on the assessment of personal insect repellent scenarios. The PMRA has based the residential exposure assessment on algorithms from the draft EPA Res SOP (EPA 2009). While this SOP is still in draft form, it was considered to be the most appropriate to characterize exposure from the use of the proposed icaridin personal insect repellent products.

3.4.2.1 Applicator Exposure and Risk

An applicator assessment was not performed as this exposure scenario was considered to be covered by the residential user assessment since any residues that would get on the skin during application are accounted for in the exposure assessment algorithm. Exposure beyond personal application could take place for adults applying personal insect repellents to young children (> 6 months). However, this exposure is considered to be minimal compared to the exposure from self-application.

3.4.2.2 Postapplication Exposure and Risk

Inhalation exposure was not quantified as the labels for the spray products stipulate that the products are not to be sprayed in enclosed places and are to be applied to the face via hand application. Furthermore, the vapour pressure that is required for an outdoor inhalation waiver is less than 1×10^{-4} kPa (NAFTA, 1999) and the vapour pressure of icaridin is 3.4×10^{-5} kPa at 20°C.

Residential dermal exposure and risk estimates were derived for adults, youth, children, toddlers and infants (> 6 months) exposed to icaridin residues from the use of pump spray, pressurized spray, and towelette personal insect repellent formulations. Exposure estimates also took into account exposure time per day, number of applications per day, and percentage of body covered by the products (Table 4 of Appendix 1).

It is acknowledged that small children (> 6 months) may be exposed via the oral route through incidental hand-to-mouth contact (Table 5 of Appendix 1). Although many of the proposed labels prohibit direct application to the hands of children, it was assumed that some of the product from treated areas of the skin could be transferred to the hands of small children and subsequent hand-to-mouth ingestion may occur.

Dermal exposures for adults and youth exceeded the target MOE of 100 for all formulations. Dermal exposures to children, toddlers and infants (> 6 months) were acceptable for pump spray, aerosol spray, and towelette formulations (Table 6 and Table 7 of Appendix 1).

A risk assessment was not performed for infants under six months of age since it is assumed that non-chemical measures can be utilized to protect this population from biting pressures. Therefore, all products carry the statement: “Do not use on infants under 6 months of age.”

3.4.2.3 Aggregate Exposure and Risk

The aggregate risks of icaridin were calculated based on the NOAEL of 301 mg/kg bw/day from the 90-day oral rat study. There are no food or water sources of exposure. Incidental oral exposure estimates for toddlers and infants (> 6 months) were generated and aggregated with the dermal exposures according to the procedures outlined in PMRA document SPN2003-04, and presented in Table 6 and Table 7 of Appendix 1. For aggregate dermal and incidental oral exposure to toddlers and infants, the MOEs for pump spray, aerosol spray and towelette formulations were considered acceptable.

3.4.2.4 Bystander Exposure and Risk

For bystanders, exposure is expected to be much less than that for users and is considered negligible. Therefore, health risks to bystanders are not of concern.

4.0 Value

4.1 Effectiveness Against Pests

4.1.1 Acceptable Efficacy Claims

4.1.1.1 Mosquitoes

Eleven studies were evaluated to support use of 10% icaridin products against mosquitoes. The data demonstrated that 10% icaridin products provided up to five hours of protection from mosquitoes.

Ten studies were evaluated to support use of 20% icaridin products against mosquitoes. The data demonstrated that 20% icaridin products provided up to seven hours of protection from mosquitoes.

4.1.1.2 Ticks

Two studies were evaluated to support use of 10% icaridin products against ticks. Based on the data submitted, protection from ticks for up to seven hours is conditionally accepted. Required data are listed later in this document.

Three studies were evaluated to support use of 20% icaridin products against ticks. The data demonstrated that 20% icaridin products provided up to eight hours of protection from ticks.

4.1.1.3 Black flies

One study was evaluated to support use of 20% icaridin products against black flies. It demonstrated protection from black flies for at least eight hours. Based on the data submitted, eight hours of protection from black flies is conditionally accepted. Required data are listed later in this document.

4.2 Non-safety adverse effects

Data were provided to support non-safety adverse effects claims for the 10% icaridin products. They demonstrated that treatment with 10% icaridin did not cause any adverse effects to garments made of polyester, polyester/rayon/spandex blend, nylon/lycra/spandex blend, cotton/nylon blend and 100% cotton. No adverse effects were observed on costume jewellery and plexiglass. Adverse effects were observed on leather, lacquered wood and hair dyes (bleeding of colour was observed).

No non-safety adverse effects data were provided for the 20% icaridin products.

4.3 Sustainability

4.3.1 Survey of Alternatives

Several products containing DEET at various concentrations are registered as personal insect repellents, providing protection against all of the pests accepted for icaridin. Products containing citronella oil are registered as personal repellents against mosquitoes; and products containing p-menthane-3,8-diol and soybean oil are registered as personal repellents against mosquitoes and black flies.

4.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

End-use products containing icaridin in the form of sprays or towellettes are easy to use and compatible with other methods used for personal protection against mosquitoes, ticks and black flies.

4.3.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

As the mode of action of end-use products containing icaridin is to repel arthropods, rather than to kill them, they will not exert selection pressure that would lead to the development of resistance.

5.0 Summary

5.1 Human Health and Safety

The submitted toxicology database is adequate to define the majority of toxic effects that may result from exposure to Icaridin Technical Insect Repellent. There was no evidence of carcinogenicity in rats or mice after longer-term dosing. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. Icaridin Technical Insect Repellent was not neurotoxic. In repeated-dose studies on laboratory animals, the primary target organs were the liver and kidney. The risk assessment protects against the toxic effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Exposure to the personal insect repellent products containing icaridin, All-Family Insect Repellent Spray, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray I and II, OFF! Active Insect Repellent Clean Feel, OFF! Deep Woods Pump Spray Insect Repellent Clean Feel, and OFF! Family Care Clean Feel Insect Repellent Towelettes, is not expected to result in unacceptable risk to any segment of the population, adults, youth, children, toddlers and infants (> 6 months), when used according to label directions.

5.2 Value

The data submitted to register All-Family Insect Repellent Spray, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent I, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent II, OFF! Active Insect Repellent Clean Feel, OFF! Deep Woods Pump Spray Insect Repellent Clean Feel and OFF! Family Care Clean Feel Insect Repellent Towelettes support their use as personal insect repellents, when used according to the directions provided on the label.

5.2.1 Unsupported Uses

- All-Family Insect Repellent Spray (containing 20% icaridin): claims against stable flies, biting midges and chiggers were not accepted due to insufficient data or rationales.

- Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent I and Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent II (containing 10% icaridin): a claim against black flies was not accepted due to insufficient data.

6.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Icaridin Technical Insect Repellent, All-Family Insect Repellent Spray, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray I, Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray II, OFF! Active Insect Repellent Clean Feel, OFF! Family Care Clean Feel Insect Repellent

Towelettes and OFF! Deep Woods Pump Spray Insect Repellent Clean Feel, containing the technical grade active ingredient icaridin, as a personal insect repellent against mosquitoes and various pests as indicated on the label.

An evaluation of available scientific information found that, under the approved conditions of use, these products have value and do not present an unacceptable risk to human health or the environment.

List of Abbreviations

ADME	absorption, distribution, metabolism and excretion
abs	absolute
a.i.	active ingredient
ALT	alanine aminotransferase
app	application(s)
AST	aspartate aminotransferase
AUC	area under the curve
bw	body weight
bwg	body weight gain
CAS	Chemical Abstracts Service
CHO	Chinese Hamster Ovary
cm	centimetre(s)
cm^2	centimetre(s) squared
DEET	N,N-Diethyl-m-toluamide
DHPW	a strain of guinea pig
DNA	deoxyribonucleic acid
EC_3	concentration required to induce a threshold positive sensitization response (SI=3)
fc	food consumption
fe	food efficiency
FOB	Functional Observation Battery
g	gram(s)
GD	gestation day
HDPE	high-density polyethylene (plastic)
hr	hour
i.v.	inter ven
IRB	independent review board
IUPAC	International Union of Pure and Applied Chemistry
kPa	kiloPascals
kg	kilogram(s)
k_{ow}	n-octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50%
LD	lactation day
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
mg	milligram(s)
mL	millilitre(s)
mm	millimetre(s)
MAS	maximum average score for 24, 48 and 72 hours
MIS	maximum irritation score
MOE	margin of exposure
MTD	maximum tolerated dose
n/a	not applicable
nm	nanometre(s)
NOAEL	no observed adverse effect level

NZW	New Zealand White
Pa	Pascale
PCPA	*Pest Control Product Act*
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
rel	relative
RH	relative humidity
SI	stimulation index
SOP	Standard Operating Procedures
UDS	Unscheduled DNA Synthesis
US EPA	United States Environmental Protection Agency
UV	ultra violet
wt	weight
♂	male
♀	female

Appendix I Tables and Figures

Table 1a Toxicity Profile of OFF! Family Care Clean Feel Insect Repellent Towelettes Containing Icaridin (Effects are known or assumed to occur in both sexes unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley rats PMRA 1513473	LD_{50} > 5050 mg/kg bw Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA 1513475	LD_{50} > 5020 mg/kg bw Low toxicity
Acute inhalation toxicity	Waived due to form of product (towelette): expected exposure via this route is negligible.
Dermal irritation NZW rabbits PMRA 1513483	MAS = 0, MIS = 0 Non-irritating
Eye irritation Mol:Russian rabbits PMRA 1513481	MAS = 29.8, MIS = 42.3 (at 24 hours). Full reversibility by 14 days. Moderately irritating
Dermal sensitization (Beuhler test) Hartley guinea pigs PMRA 1513485	Non-sensitizer

Table 1b Toxicity Profile of OFF! Deep Woods Pump Spray Insect Repellent Clean Feel Containing Icaridin (Effects are known or assumed to occur in both sexes unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley rats PMRA 1513473	LD_{50} > 5050 mg/kg bw Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA 1513475	LD_{50} > 5020 mg/kg bw Low toxicity
Acute inhalation toxicity Wistar rats PMRA 1513477	LC_{50} > 30.2 mg/L Low toxicity
Dermal irritation NZW rabbits PMRA 1513483	MAS = 0, MIS = 0 Non-irritating
Eye irritation Mol:Russian rabbits PMRA 1513481	MAS = 29.8, MIS = 42.3 (at 24 hours). Full reversibility by 14 days. Moderately irritating
Eye irritation Hra: NZW rabbits PMRA 1513479	MAS = 24.5, MIS = 31.8 (at 24 hours). Irreversible in one animal after 28 days. Moderately irritating
Dermal sensitization (Beuhler test) Hartley guinea pigs PMRA 1513485	Non-sensitizer

Table 1c Toxicity Profile of OFF! Active Insect Repellent Clean Feel Containing Icaridin (Effects are known or assumed to occur in both sexes unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley rats PMRA 1513473	LD_{50} > 5050 mg/kg bw Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA 1513475	LD_{50} > 5020 mg/kg bw Low toxicity
Acute inhalation toxicity Wistar rats PMRA 1513477	LC_{50} > 30.2 mg/L Low toxicity
Dermal irritation NZW rabbits PMRA 1513483	MAS = 0, MIS = 0 Non-irritating
Eye irritation NZW rabbits PMRA 1512701	MAS = 15.43, MIS = 25 (at 24 hours). Full reversibility by 14 days. Moderately irritating
Dermal sensitization (Beuhler test) Hartley guinea pigs PMRA 1513485	Non-sensitizer

Table 1d Toxicity Profile of All Family Insect Repellent Spray Containing Icaridin
(Effects are known or assumed to occur in both sexes unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley rats PMRA 1509731	LD_{50} > 5050 mg/kg bw Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA 1509737	LD_{50} > 5020 mg/kg bw Low toxicity
Acute inhalation toxicity Wistar rats PMRA 1509740	LC_{50} > 30.2 mg/L Low toxicity
Dermal irritation NZW rabbits PMRA 1509742	MAS = 0, MIS = 0 Non-irritating
Eye irritation NZW rabbits PMRA 1509741	MAS = 29.2, MIS = 37.3 (at 24 hours). Full reversibility by 7 days. Moderately irritating
Dermal sensitization (Beuhler test) Hartley guinea pigs PMRA 1812706	Non-sensitizer

Table 1e Toxicity Profile of Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray I and Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent Spray II Containing Icaridin (Effects are known or assumed to occur in both sexes unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Wistar rats PMRA 1510988	LD_{50} > 2000 mg/kg bw Low toxicity
Acute dermal toxicity Wistar rats PMRA 1510989	LD_{50} > 4000 mg/kg bw Low toxicity
Acute inhalation toxicity Wistar rats PMRA 1510990	LC_{50} > 5.943 mg/L Low toxicity
Dermal irritation NZW rabbits PMRA 1510997	MAS = 0, MIS = 0 Non-irritating
Eye irritation NZW rabbits PMRA 1510996	MAS = 50, MIS = 67.3 (at 1 hour). Full reversibility by 7 days. Moderately irritating
Dermal sensitization (Beuhler test) Hartley guinea pigs PMRA 1511000	Non-sensitizer

Table 2 Toxicity Profile of Technical Icaridin Technical Insect Repellent
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/ Animal/ PMRA #	Study Results
Toxicokinetics PMRA 1509317	The toxicokinetics of ^{14}C radiolabelled Icaridin were investigated in rats following a single i.v. low dose (20 mg/kg), a single dermal low dose (20 mg/kg), repeated dermal low doses (20 mg/kg bw/day) for 15 days, or a single dermal high dose (200 mg/kg). **Absorption:** Dermal absorption was similar following either a single low dose or repeated low doses, and ranged from 61-66% of the administered dose in both sexes (including radioactivity in/on the skin at the application site). A lower percentage was absorbed following a single high dose application, with 40% and 55% of the administered dose absorbed in females/ males, respectively. The amount remaining in/on the washed skin at the application site varied from 0.3% (high dose males) to 7.9% (repeated low dose males). Based on the differences in recovery of radioactivity between a single i.v. injection and dermal application of the low dose, it was assumed that evaporation of the test material through the filter paper and the protective bandage accounted for between 18-23% of the applied dermal dose over the 7 day exposure period. Dermal absorption was rapid in both sexes (half-lives of 0.8-3.4 hr), with peak plasma levels reached between six and eight hours following application of a single low dose, repeated low doses or a single high dose. Plasma concentrations were higher in females than males.
Toxicokinetics PMRA 1509317	**Excretion:** <u>i.v. dosing:</u> Rapidly eliminated, primarily in the urine. Females had higher plasma concentrations and lower clearance values than males. Total urinary excretion accounted for 74-82% of the administered dose for males and 87-90% of the dose for females, the majority of which was eliminated within 24 hours. Fecal excretion accounted for 12-17% of the dose in males and 5-6% of the dose in females. Negligible amounts were eliminated in expired air (≤0.02%) in both sexes. <u>Dermal dosing</u>: Rapidly eliminated in all dose groups, primarily in the urine, with the majority of the urinary radioactivity eliminated within 48 hours. Elimination from plasma was dose- and sex-dependent, with females having greater AUC values, lower clearance values and shorter mean residence times than males. Cumulative excretion of the test compound was similar following both single and repeated low dosing (58%-63% of the administered dose), but was reduced in the high dose group (54% and 40% of the dose in males/females, respectively). The distribution of radioactivity between urine and feces was similar for each of the dermally dosed groups. In males, urinary excretion accounted for 43-46% of the administered dose in both low dose groups, whereas females eliminated slightly more via the urine, with 55-56% of the dose was excreted via this route. Fecal excretion amounted to 12%-15% of the administered dose in males and 7% in females that received either the single or repeated low dose. At the high dose level urinary excretion accounted for only 26% (males) and 36% (females) of the administered dose, with 7% (males) and 4% (females) eliminated via the feces.

Study Type/ Animal/ PMRA #	Study Results
Toxicokinetics PMRA 1509317	**Distribution/target organ(s):** i.v. dosing: Residues in the body (excluding the gastrointestinal tract) ranged from 0.16% to 0.2% of the administered dose following i.v. dosing. Concentrations of radioactivity in organs, tissues and blood were similar between males and females, except in the liver, in which levels in males were approximately 2-fold greater than females. The highest residue levels were found in the liver, kidneys and fat. Dermal dosing: Following dermal application, the highest residues were found in the skin at the application site, with the highest value noted in males that received the repeated low dose. Residues in the body (excluding the skin at the application site and the gastrointestinal tract) ranged from 0.07% of the applied dose (high dose females) to 0.25% (low dose males). Generally, the pattern of distribution of radioactivity among tissues was similar between the sexes and dose groups. The exception was the liver, in which levels in males were approximately 1.4- to 3.2-fold greater than those in females. Aside from the skin at the application site, the highest residue levels were found in the skin, fat, liver, kidneys and lungs.
Toxicokinetics PMRA 1509317	**Toxicologically significant compound(s):** Biotransformation of Icaridin in the rat mainly followed phase I reactions resulting in metabolites hydroxylated in the piperidine ring and in the 2-methylpropyl ester side chain and those with the alcohol group oxidised to a carboxyl group. Including parent compound, 18 metabolites were identified in the urine and feces of animals of both sexes, and all dose groups. With the exception of two metabolites which were found only in feces in minor amounts (fatty acid esters of the parent compound; <0.3% of the dose), the same metabolites were identified in both urine and feces, with a similar distribution pattern. The overall metabolite pattern was similar between sexes, dose groups, and route of administration. The only difference among dose groups was that minor amounts of parent compound (0.5-1.3%) were detected in excreta of dermally dosed rats, whereas parent was not detected in the excreta of i.v. dosed animals. The most prominent metabolites were isomers of 2-(2-acetyl)-1-piperidinecarboxylic acid esterified with 1-methyl-2-hydroxypropyl alcohol, 1-hydroxymethylpropyl alcohol, or 1-methylpropyl alcohol. Together, these isomers accounted for 54% -64% of the totally excreted radioactivity in the dermally treated rats, and 52% -77% of the excreted radioactivity in the i.v. dosed groups. Parent compound and its glucuronic acid conjugates as well as other phase II metabolites were minor components.
Acute oral toxicity Wistar Rats PMRA 1509242	LD_{50} (♂) = 4743 mg/kg bw (estimated) Low Toxicity
Acute oral toxicity Wistar Rats PMRA 1509244	LD_{50} (♂) = 2236 mg/kg bw (estimated) Low Toxicity

Study Type/ Animal/ PMRA #	Study Results
Acute dermal toxicity Sprague Dawley Rats PMRA 1509246	LD_{50} (♂/♀) >2000 mg/kg bw Low Toxicity
Acute dermal toxicity Wistar Rats PMRA 1509248	LD_{50} (♂) > 5000 mg/kg bw Low Toxicity
Acute inhalation toxicity Wistar Rats (nose-only) PMRA 1509250	LC_{50} > 4.364 mg/L (♂/♀) Low Toxicity
Eye Irritation NZW Rabbits PMRA 1509252	MAS = 21.6 MIS = 27.5 at 24 hrs All scores zero by day 14 (since all scores were not zero by day 7, the hazard category is increased one level) Moderately Irritating
Eye and Skin Irritation NZW Rabbits PMRA 1509254	<u>Eye irritation:</u> MAS = 15.6 MIS = 23.3 at 1 hr Mildly irritating to the eye <u>Dermal irritation:</u> MAS = 0.22 MIS = 0.33 at 1 hr Minimally irritating to the skin
Dermal Irritation NZW Rabbits PMRA 1509256	MAS = 0 MIS = 0 Non-irritating

Study Type/ Animal/ PMRA #	Study Results
Dermal Sensitization (Buehler) DHPW Guinea Pigs PMRA 1723393, 1509258	Not a skin sensitizer
Acute oral toxicity (Acute Toxic Class) Wistar Rats KBR 8180 (N-methyl-O -ester; by-product of KBR 3023) PMRA 1509263	LD_{50} was estimated to be between 500 and 1000 mg/kg bw Moderate toxicity
14-day dietary Sprague Dawley Rats PMRA 1509270	NOAEL = 1731/1826 mg/kg bw/day **1731/1826 mg/kg bw/day:** ↓bw, bwg and fc during week one, ↑liver wt, minimal to slight liver hypertrophy, ↑cholesterol; ↑kidney wt (♂) *[none of the above effects were considered to be adverse.]*
28-day dietary Sprague Dawley Rats PMRA 1509266 (satellite study conducted with the 90-day dietary study)	NOAEL = 308/360 mg/kg bw/day **≥308/360 mg/kg bw/day:** ↑liver wt, ↑incidence of diffuse hepatocellular hypertrophy *[considered non-adverse]* **1034/1141 mg/kg bw/day:** ↓bw, ↓bwg, ↑cholesterol; ↓triglycerides, ↓glucose, ↑rel kidney wt, ↑incidence of protein droplet degenerative nephropathy (♂)
90-day dietary Sprague Dawley Rats PMRA 1509264	NOAEL = 301/382 mg/kg bw/day **≥301/382 mg/kg bw/day:** ↑incidence of diffuse hepatocellular hypertrophy, ↓triglycerides *[both findings considered non-adverse]* **1033/1192 mg/kg/bw/day:** ↓bw , ↓bwg, ↑cholesterol, ↓AST/ALT, ↑liver wt; ↑ kidney wt, ↑incidence of protein droplet degenerative nephropathy, ↓glucose (♂)

Study Type/ Animal/ PMRA #	Study Results
90-day dermal Sprague Dawley Rats PMRA 1509268	**Systemic toxicity:** NOAEL = 200 mg/kg bw/day **≥200 mg/kg bw/day:** diffuse liver hypertrophy [not considered adverse] **≥500 mg/kg bw/day:** ↓urine pH; ↑ rel kidney wt, necrosis of individual liver cells, ↑ incidence of minimal to slight hyaline degeneration in kidney tubules(♂); ↑liver wt (♀) **Dermal irritation:** NOAEL not established **≥80 mg/kg bw/day:** dose-related ↑ incidence of exfoliation, scabs, red foci, orange hue; erythema at dose site (♀), minimal to slight acanthosis, hyperkeratosis and/or sebaceous gland hypertrophy around the hair follicles *(not considered adverse-attributed to the adaptive response of the skin following the cumulative exposure to the test material)* **Recovery animals:** all compound-related changes had returned to normal at the end of the recovery period.
90-day dermal CD-1 Mice Range-finding study summarized within the mouse oncogenicity study (full study report not submitted) PMRA 1509272	Effect levels not established since the study report is considered to be supplemental. There were no treatment-related effects on body weight, food consumption, clinical observations, mortality, hematology, organ weights, gross pathology or histopathology parameters.
1-year dermal Beagle Dogs PMRA 1509285	**Systemic toxicity** NOAEL =200 mg/kg bw/day LOAEL not established **Dermal irritation** NOAEL =200 mg/kg bw/day LOAEL not established
18-month dermal oncogenicity CD-1[ICR]/BR Mice PMRA 1509272	**Systemic toxicity** NOAEL = 200 mg/kg bw/day LOAEL not established **Dermal irritation** NOAEL = 200 mg/kg bw/day LOAEL not established No evidence of carcinogenicity.
2-year dermal chronic/oncogenicity Sprague Dawley Rats PMRA 1509279	**Systemic toxicity** NOAEL = 200 mg/kg bw/day LOAEL not established **Dermal irritation** NOAEL = 200 mg/kg bw/day LOAEL not established No evidence of carcinogenicity.

Study Type/ Animal/ PMRA #	Study Results
1-generation (Pilot) dermal Reproductive toxicity Sprague-Dawley Rats PMRA 1509287	Supplemental Effect levels not established [the main purpose of the study was to refine the procedures and techniques that would be used in the main study] No treatment-related clinical signs (including signs of dermal irritation) or effects on body weight, food consumption (parental animals), litter parameters, reproductive indices or gross necropsy findings were observed in either parental animals or offspring after application of 200 mg/kg bw/day.
2-generation dermal reproductive toxicity Sprague-Dawley Rats PMRA 1509288	**Parental Toxicity:** NOAEL = 200 mg/kg bw/day LOAEL not established **≥100 mg/kg bw/day:** Scaling/sloughing of the skin at the treatment site was noted in mid- and high-dose parental animals of both generations *(not considered adverse; attributed to an adaptive response of the skin following the cumulative exposure to the test material)* **OFFspring Toxicity:** NOAEL = 200 mg/kg bw/day LOAEL not established **Reproductive Toxicity:** NOAEL = 200 mg/kg bw/day LOAEL not established No evidence of sensitivity of the young
Developmental toxicity – dermal (Range-finding) Sprague-Dawley Rats PMRA 1509295	Supplemental Effect levels not established since this was a range-finding study. Fetal assessment included only a gross external examination. Maternal liver, thyroid and uterine weights were determined. No treatment-related maternal, embryo or fetal effects were noted at dose levels up to 200 mg/kg bw/day.
Developmental toxicity – dermal (Range-finding) Sprague-Dawley Rats Study conducted to asses the physical limitations of dermal application of the test substance. PMRA 1509296	Supplemental Effect levels not established since this was a range-finding study. Fetal assessment included only a gross external examination. Maternal liver, kidney, thyroid and uterine weights were determined. Scaling/sloughing was observed at the dose site of all test substance-treated groups (dose levels of 250 to 1000 mg/kg bw/day) from approximately GD 7 until termination. No other treatment-related maternal, embryo or fetal effects were noted at any dose level. *A dose- and time-related spreading of the test material into the area surrounding the shaved dose site was apparent at all doses, suggesting that the physical limit of application is less than 250 mg/kg bw/day. However, given the short duration of a developmental toxicity study, a high dose of 400 mg/kg bw/day was proposed for the main study even though dose spreading would be substantial.*

Study Type/ Animal/ PMRA #	Study Results
Developmental toxicity – oral gavage (Range-finding) Wistar Rats PMRA 1509294	Supplemental Effect levels not established since this was a range-finding study. Dams treated with 500 mg/kg bw/day showed impairment of food and water intake, reduced excretion, and decreased body weight gain. Increased incidence of empty stomachs noted upon autopsy. Fetuses in the 500 mg/kg group exhibited a significantly increased incidence of delayed bone ossification; primarily in the vertebrae, skull and hyoid bone [litter incidence not reported].
Developmental toxicity – dermal Sprague-Dawley Rat PMRA 1509297	**Maternal Toxicity:** NOAEL = 400 mg/kg bw/day **≥50 mg/kg bw/day:** scaling and/or sloughing of the skin at the dose site (14/30 dams at 50 mg/kg bw/day and all dams at 200 and 400 mg/kg bw/day) *[not considered adverse; attributed to an adaptive response of the skin following the cumulative exposure to the test material]* **400 mg/kg bw/day:** ↑liver wt. (*not considered adverse)* A dose- and time-related spreading of the test material into the area surrounding the shaved dose site was apparent at doses of 200 and 400 mg/kg bw/day. **Developmental Toxicity:** NOAEL = 400 mg/kg bw/day LOAEL not established No evidence of malformations. No evidence of sensitivity of the young.
Developmental toxicity – dermal (Range-finding) Himalayan Rabbit PMRA 1509299	Supplemental Effect levels were not established since this was a range-finding study. Fetal assessment included only a gross external examination. Dermal reactions were evident at the dose site in all treated groups (50 - 1000 mg/kg bw/day) and appeared in a dose dependent manner. Squamous dose sites were present in all treated animals, erythema was noted in all treated groups (severity increased with increasing dose), edema was present at doses ≥400 mg/kg bw/day, cracked skin was evident in two animals at 400 mg/kg bw/day and in all animals that received ≥700 mg/kg bw/day). At 1000 mg/kg bw/day two dams were sacrificed for humane reasons (GD 9 and 14) following severe body weight loss. These dams were not pregnant. The third dam also lost weight until GD 16. Decreased food consumption was noted in all animals. Gastrointestinal changes were noted in one of the sacrificed dams upon necropsy. The surviving female showed a marginally increased number of resorptions compared to the mean number in controls. <u>Note:</u> spreading of the test material was evident in a dose-dependent manner for the 200 and 400 mg/kg bw/day groups. Severe lesions formed at the dose site for the 700 and 1000 mg/kg bw/day groups, and the test material was absorbed into the lesions (thus spreading of the test material was not apparent at these doses).

Study Type/ Animal/ PMRA #	Study Results
Developmental toxicity – dermal Himalayan Rabbit PMRA 1509301	**Maternal Toxicity:** NOAEL = 200 mg/kg bw/day LOAEL not established **≥50 mg/kg bw/day:** dermal reactions noted at the dose site in a dose-dependent manner (erythema, squamous and cracked skin) **Developmental Toxicity:** NOAEL = 200 mg/kg bw/day LOAEL not established No evidence of malformations. No evidence of sensitivity of the young.
In vitro bacterial gene mutation assay PMRA 1509303	Negative.
In vitro gene mutation assay - CHO cells PMRA 1509305	Study considered unacceptable. Inconsistencies in data and study conduct.
In vitro gene mutation assay - Chinese hamster V79 cells PMRA 1509309	Negative.
In vitro chromosome aberration assay - CHO cells PMRA 1509307	Positive with metabolic activation. Equivocal without metabolic activation.
In vitro chromosome aberration assay - CHO cells PMRA 1509311	Negative.
In vivo mammalian cytogenetics assay – mouse micronucleus PMRA 1509312	Negative.
UDS Assay – rat hepatocytes PMRA 1509314	Negative.

Study Type/ Animal/ PMRA #	Study Results
In vitro bacterial gene mutation assay KBR 8180 (N-methyl-O-ester; by-product of KBR 3023) PMRA 1509316	Negative.
Acute dermal neurotoxicity Fischer 344 Rats PMRA 1509290	**Systemic toxicity:** NOAEL = 2000 mg/kg bw LOAEL not established **Dermal irritation:** NOAEL = 2000 mg/kg bw LOAEL not established
90-day dermal neurotoxicity Fischer 344 Rats PMRA 1509292	**Systemic toxicity:** NOAEL = 200 mg/kg bw/day LOAEL not established **Dermal irritation:** NOAEL = 200 mg/kg bw/day LOAEL not established
Special Studies Investigating the Use of Rodent Jackets	
Fischer 344 Rats PMRA 1509290	A series of studies were conducted in order to investigate the use of "rodent jackets" in the acute neurotoxicity study. These studies were aimed at determining the following: the effectiveness of the jackets in limiting animal access to the dose site and establishing any clinical signs associated with their use, the impact of the rodent jackets on the FOB and automated measures of activity, and the impact of the jackets on the sensitivity of the test procedures in the detection of a treatment-related decrease in activity. The jackets were effective in limiting the animal's access to the dose site. The associated clinical signs were minimal (nasal, perianal lacrimal and oral staining), however levels of activity in the figure-8 maze were substantially reduced. The study results indicated that the procedure was sensitive in detecting a treatment-related decrease in activity in both male and female rats.

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Icaridin

Exposure Scenario	Study	Point of Departure and Endpoint	Target MOE[1]
Short- to intermediate – term dermal, non-dietary oral ingestion, aggregate	90-day dietary rat	NOAEL = 301 mg/kg bw/day	100

[1]MOE refers to a target Margin Of Exposure (MOE) for occupational and residential assessments.

Table 4 Post-Application Dermal Exposure Parameters

AR_P	Product- Specific Application Rate[1]	0.79 mg product/cm^2 (Pump Spray); 1.12 mg product/cm^2 (Aerosol); 1.14 mg product/cm^2 (Towelette)
F_{AI}	Product Guarantee	10 – 20%
ET	Exposure Time[2]	12 hr/day
AppF	Application Frequency[3]	0.14 – 0.2 app/hr
F_{Body}	% Body Exposed[4]	31% (short sleeve-shirt, shorts, socks and shoes)

[1]Application Rate from efficacy studies (pump spray) and Default EPA Residential SOP (EPA, 2009) (aerosol, towelette)
[2]Appropriate exposure time determined by the PMRA
[3]Application frequency based on product-specific protection time (e.g., 1 application/5 hour protection time = 0.2 applications/hr)
[4]% body exposed is medium level scenario from draft EPA Residential SOP (EPA, 2009)

Table 5 Post-Application Incidental Oral Exposure Parameters

HR	Hand Residue Loading[1]	AR_P* F_{AI} = (mg product/ cm^2) * (% ai)
F_M	Fraction Hand Surface Mouthed[2]	12.7%
SA_H	Surface Area Hand[3]	225 cm^2
ET	Daily Exposure Time[4]	12 hr/day
nRepl	Replenishment Intervals per hour[5]	0.14 – 0.2 app/hr
SE_H	Saliva Extract. Factor[6]	50%
Freq_Repl	# HTM Events per hour[7]	Toddlers : 8.4; Infants: 14.5

[1]Application rates as described in Table 3.4 and product specific guarantee
[2]Fraction of hand mouthed from draft 2009 EPA Residential SOP (EPA, 2009; arithmetic mean)
[3]Surface area of hand from 1997 EPA Residential SOP (EPA, 1997)
[4]Daily exposure time considered the same as dermal exposure time as events co-occur
[5]Replenishment intervals based on product-specific protection time (e.g., 1 application/5 hour protection time = 0.2 applications/hr)
[6]Saliva extraction factor from 2001 EPA Residential SOP Updates (EPA, 2001)
[7]Hand-to-Mouth (HTM) events per hour based on: For toddlers - draft 2009 EPA Residential SOP (EPA, 2009; arithmetic mean); For infants – EPA Child-Specific Exposure Factors Handbook (EPA, 2008; mean of means)

Table 6 Post-Application Exposure Estimates for Mosquito Control Formulations

Formulation	Guarantee	Adult	Youth	Child	Toddler			Infant (> 6 months)		
		Dermal[1]			Dermal[1]	Oral[2]	Aggregate[3]	Dermal[1]	Oral[2]	Aggregate[3]
Pump Spray	20%	0.88	1.09	1.30	1.47	0.52	1.99	1.54	0.77	2.32
Aerosol	10%	0.88	1.08	1.29	1.46	0.51	1.97	1.53	0.77	2.30
Towelette	20%	1.28	1.57	1.88	2.12	0.74	2.87	2.23	1.12	3.35
Pump Spray	10%	0.62	0.76	0.91	1.03	0.36	1.39	1.08	0.54	1.62

[1] Dermal Exposure (mg/kg bw/day) = AR_P * F_{AI}* ET * AppF * SA/BW * F_{Body} (EPA, 2009)
[2] Incidental Oral Exposure (mg/kg bw/day) = $[HR*(F_M*SA_H)(ET * nRepl)(1- (1-SE_H)^{(Freq\_Repl/nRepl)})]/BW$ (EPA, 2009)
[3] Aggregate Exposure (mg/kg bw/day) = Dermal Exposure (mg/kg bw/day) + Oral Exposure (mg/kg bw/day)

Table 7 Post-Application MOEs for Mosquito Control Formulations

Formulation	Guarantee	Adult	Youth	Child	Toddler			Infant (> 6 months)		
		Dermal			Dermal	Oral	Aggregate	Dermal	Oral	Aggregate
Pump Spray	20%	340	276	231	205	583	152	195	389	130
Aerosol	10%	343	278	233	206	588	153	196	392	131
Towelette	20%	236	191	160	142	404	105	135	270	90
Pump Spray	10%	486	394	330	293	833	217	278	556	185

Note: **Bolded** values are MOEs that are of concern; less than the target MOE of 100
Note:Target MOE = 100. Calculated MOE = NOAEL / Total Daily Exposure (mg/kg bw/day); NOAEL of 301 mg/kg bw/day from 90 day oral rat study was used for all durations and both dermal and oral routes

Table 8 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Applicant	Product	Applicant proposed label claims	Accepted label claims	Unsupported label claims
Lanxess Inc.	All-Family Insect Repellent Spray	Mosquitoes- 8 hr Ticks- 8 hr Black flies- 8 hr Stable flies- 8 hr Biting midges- 8 hr Chiggers- 8hr	Mosquitoes- 7 hr Ticks- 8 hr Black flies- 8 hr	Stable flies- 8 hr Biting midges- 8 hr Chiggers- 8hr
Avon Canada Inc.	Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent I	Mosquitoes- 7hr Ticks- 7 hr Black flies- 4hr	Mosquitoes- 5hr Ticks- 7 hr	Black flies- 4hr
	Avon Skin-So-Soft SSS Bug Guard Plus Icaridin Insect Repellent II	Mosquitoes- 8hr Ticks- 12 hr Black flies- 5hr	Mosquitoes- 5hr Ticks- 7 hr	Black flies- 4hr
S.C. Johnson and Son	OFF! Active Insect Repellent Clean Feel	Mosquitoes- 6hr	Mosquitoes- 5hr	n/a
	OFF! Deep Woods Pump Spray Insect Repellent Clean Feel	Mosquitoes- 8hr Ticks- 8hr	Mosquitoes- 7hr Ticks- 8hr	n/a
	OFF! Family Care Clean Feel Insect Repellent Towelettes	Mosquitoes- 8hr Ticks- 8hr	Mosquitoes- 7hr Ticks- 8hr	n/a

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
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1509240	2007, Product Chemistry of Icaridin Technical, DACO: 2.0,2.1,2.10,2 .11,2.11.1,2.11.2,2.11.3,2.11.4,2.12,2.12.1,2.12.2,2.13,2.13.1,2.13.2,2.13.3,2.13.4 CBI
1509241	2007, Product Chemistry of Icaridin Technical, DACO: 2.14,2.14.1, 2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7, 2.14.8,2.14.9
1811252	2009, 2.13.3 Batch Data--New York Site, DACO: 2.13.3
1811254	2008, 2.13.3 Batch Data--Dormagen site, DACO: 2.13.3
1811255	2008, 2.13.3 Batch Data CBI--Dormagen site, DACO: 2.13.3 CBI
1811257	2009, 2.13.3 Batch Data---New York Site, DACO: 2.13.3
1811258	2009, 2.13.3 Batch Data CBI---New York Site, DACO: 2.13.3 CBI
1811259	2009, 2.13.1 Methodology/Validation, DACO: 2.13.1
1811260	2009, 2.15 Sample of Chemical Standard, DACO: 2.15
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1812704 2007, Storage Stability Test: 12 Months at 25 C (60% rel. humidity), DACO: 3.5.10

1513434 Description of Starting Materials, DACO: 3.2.1

1513437 Description of Starting Materials - CBI, DACO: 3.2.1 CBI

1513439 Formulation process - CBI, DACO: 3.2.2 CBI

1513441 Formulation process, DACO: 3.2.2

1513442 Formulation of impurities, DACO: 3.2.3

1513444 Establishing Certified Limits - CBI, DACO: 3.3.1 CBI

1513446 Establishing Certified Limits, DACO: 3.3.1

1513448 Analytical Method, DACO: 3.4.1

1513450 Analytical Method - CBI, DACO: 3.4.1 CBI

1513452 Impurities of toxicological concern, DACO: 3.4.2

1513453 phys/chem, DACO: 3.5 CBI

1513454 Colour, DACO: 3.5.1

1513455 stability, DACO: 3.5.10

1513456 stability - CBI, DACO: 3.5.10 CBI

1513457 flammability, DACO: 3.5.11

1513458 explodability, DACO: 3.5.12

1513459 Miscibility, DACO: 3.5.13

1513460 Corrosion, DACO: 3.5.14

1513461 Dielectric Breakdown Voltage, DACO: 3.5.15

1513463 Physical State, DACO: 3.5.2

1513464 Odour, DACO: 3.5.3

1513465 Formulation Type, DACO: 3.5.4

1513466 Container, DACO: 3.5.5

1513467 Density/Specific Gravity, DACO: 3.5.6

1513468 pH, DACO: 3.5.7

1513469 Oxidizing or Reducing action, DACO: 3.5.8

1513470 Viscosity, DACO: 3.5.9

1819820 Updated certified limits, DACO: 3.3.1 CBI

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1819824 Corrosion characteristics deficiency response, DACO: 3.5.14

1512670 Description of Starting Materials, DACO: 3.2.1

1512671 Description of Starting Materials - CBI, DACO: 3.2.1 CBI

1512672 Formulation process - CBI, DACO: 3.2.2 CBI

1512673 Formulation process, DACO: 3.2.2

1512674 Formulation of impurities, DACO: 3.2.3

1512675 Establishing Certified Limits - CBI, DACO: 3.3.1 CBI

1512676 Establishing Certified Limits, DACO: 3.3.1

1512677 Analytical Method, DACO: 3.4.1

1512678 Analytical Method - CBI, DACO: 3.4.1 CBI

1512679 Impurities of toxicological concern, DACO: 3.4.2

1512680 phys/chem, DACO: 3.5 CBI

1512681 Colour, DACO: 3.5.1

1512682 stability, DACO: 3.5.10

1512683 flammability, DACO: 3.5.11

1512684 explodability, DACO: 3.5.12

1512685 Miscibility, DACO: 3.5.13

1512686 Corrosion, DACO: 3.5.14

1512687 Dielectric Breakdown Voltage, DACO: 3.5.15

1512688 Physical State, DACO: 3.5.2

1512689 Odour, DACO: 3.5.3

1512690 Formulation Type, DACO: 3.5.4

1512691 Container, DACO: 3.5.5

1512692 Density/Specific Gravity, DACO: 3.5.6

1512693 pH, DACO: 3.5.7

1512694 Oxidizing or Reducing action, DACO: 3.5.8

1512695 Viscosity, DACO: 3.5.9

1819938 Updated certified limits, DACO: 3.3.1 CBI

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1819942 Final Report for the Validation of Quantitative Analytical Method ARTM-W-212710 to determine the concentration of KBR 3023 in aerosol repellent product, DACO: 3.4.1 CBI

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1513645 Description of Starting Materials, DACO: 3.2.1

1513646 Description of Starting Materials - CBI, DACO: 3.2.1 CBI

1513647 Formulation process - CBI, DACO: 3.2.2 CBI

1513648 Formulation process, DACO: 3.2.2

1513650 Formulation of impurities, DACO: 3.2.3

1513651 Establishing Certified Limits - CBI, DACO: 3.3.1 CBI

1513652 Establishing Certified Limits, DACO: 3.3.1

1513653 Analytical Method, DACO: 3.4.1

1513654 Analytical Method - CBI, DACO: 3.4.1 CBI

1513655 Impurities of toxicological concern, DACO: 3.4.2

1513656 2006, phys/chem, DACO: 3.5 CBI

1513657 Colour, DACO: 3.5.1

1513658 stability, DACO: 3.5.10

1513659 flammability, DACO: 3.5.11

1513660 explodability, DACO: 3.5.12

1513661 Miscibility, DACO: 3.5.13

1513662 Corrosion, DACO: 3.5.14

1513663 Dielectric Breakdown Voltage, DACO: 3.5.15

1513664 Physical State, DACO: 3.5.2

1513667 Odour, DACO: 3.5.3

1513668 Formulation Type, DACO: 3.5.4

1513669 Container, DACO: 3.5.5

1513670 Density/Specific Gravity, DACO: 3.5.6

1513671 pH, DACO: 3.5.7

1513672 Oxidizing or Reducing action, DACO: 3.5.8

1513673 Viscosity, DACO: 3.5.9

1819792 Updated certified limits, DACO: 3.3.1 CBI

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1819796 Corrosion characteristics response, DACO: 3.5.14

1895183 Storage stability clarifax response, DACO: 3.5.10

1895185 CBI cross reference (formula comparison), DACO: 3.5.10 CBI

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2.0 Human Health

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1509250	1990, KBR 3023: Study of the Acute Inhalation Toxicity in the Rat to OECD guideline No 403, DACO: 4.2.3
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