INFOTOX (Pty) Ltd

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Retrieval and scientific interpretation of ecotoxicological information

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Project conducted on behalf of
ADAMA South Africa (Pty) Ltd

Toxicological Risk Assessment for the Purpose of Derogation of WARLOCK® 19.2 EC
Substance of Concern: N-Methyl-2-Pyrrolidone

Report No 050-2024 Rev 1.0

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31 December 2024

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Expertise and Declaration of Independence

This report was prepared by INFOTOX (Pty) Ltd (“INFOTOX”). Established in 1991, INFOTOX is a professional scientific company, highly focused in the discipline of ecotoxicological risk assessment. Both occupational and environmental human health risks, as well as risks to ecological receptors, are addressed.

Dr Willie van Niekerk, Managing Director of INFOTOX, has BSc, Hons BSc and MSc degrees from the University of Potchefstroom and a PhD from the University of South Africa. He is a Qualified Environmental Professional (Environmental Toxicologist QEP), certified by the Institute of Professional Environmental Practice (“IPEP”) in the USA (No 07960160), and a registered Professional Natural Scientist (Pr Sci Nat, Environmental Science, No 400284/04). Dr Van Niekerk has specialized

in chemical toxicology and human health risk assessments, but he has experience in many other areas in the disciplines of analytical and environmental sciences.

Dr Marlene Fourie has BSc and Hons BSc degrees from the University of Stellenbosch and MSc and PhD degrees from the University of Pretoria. Her field of specialisation is reproductive biology/toxicology. Dr Fourie also has an MSc-degree in epidemiology from the University of Pretoria. Following positions as Medical Natural Scientist at the Andrology Unit, Department of Urology, University of Pretoria and the Pretoria Academic Hospital from 1987 to 2001, she joined INFOTOX as a Medical Biological Scientist. Dr Fourie has conducted many health risk assessments and projects relating to the health status of communities. She is registered as a Professional Natural Scientist (Pr Sci Nat, Toxicological Science, No 400190/14).

Dricky Simpson has a higher diploma in Quality Assurance as well as in Medical Technology. Dricky worked in pathology laboratories and she has done research in human toxicology and pharmacology. She also has experience in animal toxicology and pharmacology. During the last fifteen years as Director of INFOTOX she worked in human health risk assessment for a wide range of industries.

This specialist report was compiled for ADAMA South Africa (Pty) Ltd. We do hereby declare that we are financially and otherwise independent of ADAMA South Africa (Pty) Ltd.

Signed on behalf of INFOTOX (Pty) Ltd, duly authorized in the capacity of Managing Director:

Willem Christiaan Abraham van Niekerk

31 December 2024

Internal review
MH Fourie PhD (Reproductive Biology) MSc (Epidemiology) Pr Sci Nat (Toxicological Science)

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List of Abbreviations

AEL	Acceptable exposure level
AHS	Agricultural Health Study
ATSDR	Agency for Toxic Substances and Disease Registry
AWRI	Australian Wine Research Institute
BCF	Bioconcentration factor
BEAD	Biological and Economic Analysis Division
CDC	Centers for Disease Control and Prevention
CMR	Carcinogenicity, mutagenicity, and reproductive toxicity
EC	European Community
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemical's
ECHA	European Chemicals Agency
EDSP	Endocrine Disruptor Screening Program
EFSA	European Food Safety Authority
EIIS	Ecological Incident Information System
ERC	Ecological Risk Classification
FFDCA	Federal Food, Drug, and Cosmetic Act
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HHRA	Human health risk assessment
IDS	Incident Data System
IPCS	International Programme on Chemical Safety
LOAELs	Lowest-observed-adverse-effect levels
LOC	Level of concern
MOE	Margin of exposure
MRIDs	Master Record Identifiers
NIOSH	National Institute for Occupational Safety
NMP	N-Methyl-2-pyrrolidone
NOAELs	No-observed-adverse-effect levels
NRC	US National Research Council
OECD	Organisation for Economic Co-operation and Development
OPP	USEPA Office of Pesticide Programs
PAD	Population adjusted dose (a = acute, c = chronic)
PHI	Pre- harvest interval
POD	Point of departure
REACH	Registration, evaluation and authorization of chemical
RfD	Reference dose
RQ	Risk quotient
SENSOR	Health Sentinel Event Notification System for Occupational Risk-Pesticides
STOT RE	Specific target organ toxicity (repeated exposure)
TC	Transfer coefficient for the transfer of spray ingredient residues on crops and foliage to the skin of re-entry workers, or for the inhalation of volatile residues present on crops and foliage.

TRA	Targeted Risk Assessment
TRV	Tree Row Volume
TSCA	Toxic Substances Control Act
TTR	Total toxic residue
UCR	Unit Canopy Row
UF	Uncertainty factors
UFA	Uncertainty in extrapolating animal data to humans
UFH	Variation in susceptibility among the members of the human population
UFL	Uncertainty in extrapolating from a LOAEL rather than from a NOAEL
USEPA	United States Environmental Protection Agency
VSP	Vertical shoot position (for vines)

List of Terms

Abiotic hydrolysis	Degradation of chemical substances by processes not involving biological systems, e.g., breakdown by ultraviolet light interaction, not by microbiological activity.
Aerobic metabolism	Metabolism, including the production of cellular energy, with the consumption of oxygen.
Anaerobic metabolism	Metabolism, including the production of cellular energy, in the absence of oxygen.
Aqueous photolysis	Breakdown of chemical substances in an aqueous solution, by interaction with light.
Carcinogenicity	Substance that causes cancer.
Derogation	An exemption from or relaxation of the consideration of this product for removal from the market due to it being considered a CMR product of concern.
Developmental toxicity	Any developmental malformation of the foetus, caused by a toxic substance. that is caused by the toxicity of a chemical or pathogen.
Dose-response assessment	Addresses the relationship between levels of uptake of a substance and the degree of manifestation of adverse effects.
Environmental Fate	Behaviour in or movement of a chemical substance after having been released to the environment. The behaviour in or movements through the environmental compartments of air, soil and water, and the preferred final destiny compartment(s) are described.
Epidemiology	Study of the determinants, occurrence, and distribution of health and disease in a defined population.
Exposure assessment	Identification of environmental pathways, potentially exposed groups, routes of direct and indirect exposure, and estimates of concentrations and duration of exposure.
Haematopoietic system	Physiological system involved in the production and maturation of blood cells.
Half-life	The time needed for the removal of 50% of the original concentration of a substance in the environment.
Hazard assessment	The identification of the chemical constituents of potential concern and the hazards posed by these chemicals.
Hydrolysis	Involvement of water molecules in the breakdown of chemical bonds in chemical substances.
Microbial degradation	Breakdown of chemical substances by microorganisms, or their enzymes.
Mutagenicity	Property of chemical agents to induce genetic mutations.
Pathways of exposure	The sequence of environmental compartments of air, soil, water, and/or sediment, through which a substance may be distributed or spread in the environment.

Photodegradation	Breakdown of chemical substances by interaction with light.
Receptors	People exposed to the substance of interest.
Registrar	Registrar of the fertilisers, farm feed, agricultural remedies and stock remedies Act, 1947 (Act 36 of 1947) in Department of Agriculture, Land Reform and Rural Development
Reproductive toxicity	A substance or agent that can cause adverse effects on the reproductive system, causing the inability to reproduce offspring
Risk characterisation	Integration of the components described above. The risk characterisation will also provide a review of documented human exposure incidents
Routes of exposure	Inhalation, ingestion, and dermal contact
Surrogate	A chemical with properties, including potential toxicity, that are likely to be similar to another substance of interest for which little information about the properties and/or toxicity are known. "Transferring" the known properties of the surrogate to that of the uncharacterised substance is known as the "bridging principle", or "read-across" for the purposes of hazard and risk assessment.
Target organ toxicity	The effects on the organ impacted by a hazardous substance
Uncertainty review	Identifies the nature and, when possible, the magnitude of the uncertainty and variability inherent in the characterisation of risks

Executive Summary

This document is an independent risk assessment report supporting an application for derogation allowing the restricted use of the registered insecticide WARLOCK® 19.2 EC, with Act No. 36 of 1947 registration number L9872.

WARLOCK® 19.2 EC is identified as a substance of concern due to its classification as a reproductive hazard category 1B (H360D) according to the Globally Harmonized System of Classification and Labelling of Chemicals (“GHS”). The classification is due to the ingredient n-methyl-2-pyrrolidone (“NMP”), of which the GHS classification is reproductive toxicity category 1B (H360D).

Prepared for: ADAMA South Africa (Pty) Ltd
Product name: WARLOCK® 19.2 EC
Act No. 36 of 1947 registration number: L9872

Intended product use:

- An emulsifiable concentrate insecticide with stomach action for the control of the pests as listed on apples and pears, citrus, groundnuts, maize and sweetcorn, pomegranates, stone fruit, sunflowers, tomatoes, table and wine grapes.
- The product is intended for use in large-scale agricultural crop production enterprises. The large-scale farming application method is groundboom broadcast spraying.
- The product is not intended for sale to residential gardeners. This means that it will not be sold to the public on the shelves of local nurseries or general gardening stores. Therefore, domestic home garden use is excluded.
- Use of the product by small-scale farmers is not excluded, and backpack application with a hand-held spray wand is assessed for this scenario.
- The product supplier has indicated that the insecticide is not intended for aerial application (e.g., by low-flying aircraft) and this method of application is excluded from the assessment.

Occupational exposure assessment:
Two occupational designations are assessed:

- Occupational pesticide handlers, exposed by the dermal and inhalation routes of exposure (Table 1).
- Significant post-application (re-entry) worker exposure is mainly by the dermal route only.
- Inhalation exposure of post-application workers is considered negligible and is not assessed, because:
    - Label instructions are to enter only after applied product has dried off.
    - NMP is volatile; therefore, a minimum of volatile foliar/crop residues should remain at the time of re-entry, and the minimal residue should be insufficient to pose a risk of inhalation exposure to post-application workers.

Table 1: Occupational exposure profile: all crops.

Type of worker	Exposure duration	Inhalation exposure	Dermal exposure	Oral exposure
Occupational pesticide handlers: mixing/loading/spraying	Short-term (1 to 30 days)	✔	✔	N.a.
	Intermediate-term (1 to 6 months)	✔	✔	N.a.
Post-application workers: Re-entry activities	Short-term (1 to 30 days)	N.a.	✔	N.a.
	Intermediate-term (1 to 6 months)	N.a.	✔	N.a.

Completely mechanised post-application re-entry activities are highly unlikely to be associated with any significant exposure to workers and are not assessed.

Dietary exposure to treated crops

NMP is currently approved in the USA for use as a solvent inert ingredient in pesticide formulations for food applications, and is exempt from the requirements of a tolerance limit, i.e., a maximum allowable residue limit (40 CFR Part 180.920). These decisions considered developmental and reproductive effects of NMP. The exemption was reassessed several times, in 2006, 2018 and 2020, and confirmed at each assessment. This exemption infers with reasonable certainty that no harm will result from aggregate exposures to the NMP pesticide residue associated with dietary exposure and all other non-occupational exposures. According to the international Organisation for Economic Co-operation and Development ("OECD"), this conclusion is directly related to NMP's low acute toxicity, and its physical/chemical and environmental fate properties: NMP is readily biodegradable and the bioaccumulation potential in biota is expected to be very low. It is reasonable to accept that the human dietary risk assessment for NMP will not be different in South Africa.

Health risk assessment results and conclusion

- Levels of NMP to which operators are exposed when mixing and loading WARLOCK® 19.2 EC solutions for application by groundboom broadcast spraying, according to the label instructions, are not associated with a risk to health (including reproductive health). Groundboom broadcast application activities are also not associated with a risk to health.

- Small-scale farming WARLOCK® 19.2 EC application by backpack and hand-held wand was assessed. The activity of sequential mixing, loading and backpack application of the insecticide is not associated with a risk to health (including reproductive health).

- Post-application re-entries after the foliage and crops have dried (assumed at least 12 hours after application), according to product label instructions, are not associated with a risk to health (or reproductive effects).

Ecological risks

NMP has a low hazard profile for ecological receptors, and it exhibits low persistence and bioaccumulation if released into aquatic or terrestrial compartments. NMP is assessed as of low acute and chronic toxicity to aquatic organisms and birds, based on study data evaluated as of high quality. No further evaluation of ecological risks is required. NMP is known to be highly toxic to larval honey bees; therefore, adherence to the use restriction on the WARLOCK® 19.2 EC label is vital: "*Do not use WARLOCK® 19.2 EC during flowering and when bees are actively foraging, as the product can be toxic to bees*."

Restricted use application

The restricted use applied for is according to the intended product use:

- Insecticide not for sale to or used by residential gardeners.
- Preparation and application of the spray solution in accordance with the instructions on the product label.
- Personal hygiene instructions on the SDS must be followed; that is, "*wash face, hands and any exposed skin thoroughly after handling*", "*Do not eat, drink or smoke when using this product*", etc.
- Double-layered clothing must be worn when mixing/loading or applying the product; that is, a coverall over basic clothing and chemical-resistant gloves and shoes (e.g., rubber boots).
- Respiratory protection shall be used when mixing/loading or applying the product.
- Label re-entry instructions must be followed, namely, to enter only after applied product has dried off the treated crop and foliage.

- Adherence to the use restriction on the WARLOCK® 19.2 EC label is vital: "*Do not use WARLOCK® 19.2 EC during flowering and when bees are actively foraging, as the product can be toxic to bees*."

1 Background

In a document circulated to "All Regulatory Holders" on 14 April 2022, the Registrar: Act 36 Of 1947, of the Department of Agriculture, Land Reform and Rural Development ("Registrar" and "The Department") refers to an assessment that was carried out at the international level to determine risks to human health due to exposure to active ingredients and their formulations that meet the criteria of carcinogenicity, mutagenicity, and reproductive toxicity ("CMR") categories 1A or 1B according to the Globally Harmonized System of Classification and Labelling of Chemicals ("GHS"). The Department then stated that "*the assessment identified the need to reduce risks to human health associated with such products*".

Category 1A covers substances that are known to be CMR, mainly according to human evidence. Category 1B covers substances presumed to be CMR based on data from animal studies.

The Registrar stated his intention to "*prohibit the use of ingredients and their formulations that meets* (sic) *the criteria of CMR categories 1A or 1B of the GHS as from 01 June 2024*".

However, in exceptional circumstances, the Registrar may grant registration of an implicated agricultural remedy when it can be demonstrated that:

"a) The risk to humans, animals or the environment from exposure to the active substance in an agricultural remedy, under realistic worst-case conditions of use, is negligible"
(and other conditions not relevant to this INFOTOX report).

In February 2024, the Registrar issued a Guideline for the Application for a Derogation for an Agricultural Remedy Identified as a Substance of Concern.

This INFOTOX report deals with the assessment of risk to humans, animals and the environment associated with the use of WARLOCK® 19.2 EC, with the solvent N-methyl-2-pyrrolidone ("NMP") identified as a substance of concern. This is explained in the hazard assessment of the constituents of WARLOCK® 19.2 EC in Section 4. WARLOCK® 19.2 EC is an emulsifiable concentrate insecticide with stomach action for the control of the pests as listed on apples and pears, citrus, groundnuts, maize and sweetcorn, pomegranates, stone fruit, sunflowers, tomatoes, table and wine grapes.

2 Deployment of this INFOTOX document

This INFOTOX report covers various aspects of the study in logical sections, as outlined below:

Section 1 states the intention of the Department to prohibit the use of ingredients and their formulations that meet the criteria for CMR categories in a notice dated 14 April 2022 ("Notice"). The Notice defines the point of departure for this INFOTOX study.

Section 2 (this section) outlines the deployment of this report, providing context of a particular section in the overall presentation.

Section 3 describes the composition of WARLOCK® 19.2 EC.

Section 4 provides hazard information for WARLOCK® 19.2 EC and ingredients according to the GHS.

Section 5 provides a summary and describes the environmental fate assessment for NMP.

Section 6 explains the insecticide action and benefits assessment of WARLOCK® 19.2 EC.

Section 7 describes essential, concise steps of the health risk assessment paradigm.

Section 8 provides an overview of the human health risk assessment methodology.

Section 9 summarises toxicological reviews of NMP.

Section 10 provides a short summary of NMP human dietary risk assessment (food and water).

Section 11 deals with human incident reports associated with exposure to NMP.

Section 12 provides information on NMP ecological risk assessments.

Section 13 presents a summary of ecological incidents.

Section 14 explains and discusses NMP occupational exposure and risk calculations, and presents the risk results.

Section 15 presents a discussion and interpretation of the occupational risk results.

Section 16 entails a summary of the risk assessment conclusions.

Section 17 presents recommendations following from the INFOTOX study.

Section 18 lists the scientific literature references that were consulted in compiling this document.

Annexure 1 presents post-application agricultural workers residue transfer coefficients, used in occupational exposure calculations.

3 Composition of WARLOCK® 19.2 EC

The chemical composition of WARLOCK® 19.2 EC is presented in Table 3.1. The information is as presented on the product label. For two of the constituents, only EC numbers were provided. INFOTOX retrieved Chemical Abstract Service ("CAS") numbers from the open-source databases of the European Chemical Agency ("ECHA").

Table 3.1: Chemical composition of WARLOCK® 19.2 EC.

Chemical constituent	Weight %	EC and CAS numbers
Hydrocarbons, C10, aromatics, <1% naphthalene	> 60	EC 918-811-1; CAS 1189173-42-9
N-Methyl-2-pyrrolidone (NMP)	10 - 30	CAS 872-50-4
Benzenesulfonic acid, C10-13-(linear)alkyl derivatives, calcium salt	< 10	EC 932-231-6; CAS 1335202-81-7
2-Ethylhexan-1-ol	< 10	CAS 104-76-7
Emamectin-benzoate	< 10	CAS 155569-91-8
2,6-di-Tert-butyl-p-cresol	< 10	CAS 128-37-0

4 Hazard identification

4.1 The need for GHS classification

Internationally, there is a demand for safer chemicals and technologies, and it is appropriate to utilise information in the GHS as a starting point. This INFOTOX report relates specifically to ingredients and that meet the criteria of CMR categories 1A or 1B in the GHS. GHS classifications are hazard data, not risk assessments. N-Methyl-2-pyrrolidone ("NMP") is not an active ingredient of WARLOCK® 19.2 EC, but is a solvent often used in agricultural pesticides because it is compatible with most hydrophobic solvents while not affecting the emulsification properties of the main solvents. NMP is classified as a reproductive toxicity hazard, category 1B (H360D), causing the classification of WARLOCK® 19.2 EC in the same category, identifying the product as a substance of concern, as indicated in Table 4.2.1 below.

4.2 Hazard classification of constituents of WARLOCK® 19.2 EC

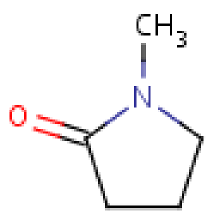
GHS classifications of the constituents of WARLOCK® 19.2 EC are presented in Table 4.2.1. INFOTOX consulted the ECHA Classification and Labelling Inventory ("C&L inventory") for GHS hazard information. The database contains relevant toxicity and other scientific data submitted to the European Community ("EC") in compliance of legal requirements for information on hazardous chemical substances. INFOTOX also consulted the official GHS guidance document (the "Purple Book", GHS 2023) to confirm hazard statement codes, hazard statements and hazard pictograms.

Table 4.2.1: GHS hazard classification of constituents of WARLOCK® 19.2 EC, with hazard statement codes, hazard statements, and pictograms.

Hazard class and category	Hazard statement code	Hazard statement	Signal word	Pictogram
Hydrocarbons, C10, aromatics, <1% naphthalene EC No 918-811-1, CAS # 1189173-42-9				
Asp. Tox. 1	H304	May be fatal if swallowed and enters airways	Danger	
STOT SE 3 (Narcosis, CNS)	H336	May cause drowsiness or dizziness	Warning	
Aquatic Chronic 2	H411	Toxic to aquatic life with long lasting effects	No signal word	
N-Methyl-2-pyrrolidone CAS # 872-50-4				
Skin Irrit.2	H315	Causes skin irritation	Warning	
Eye Irrit,2	H319	Causes serious eye irritation		
STOT SE 3	H335	May cause respiratory irritation		
Repr. 1B	H360D	May damage the unborn child	Danger	
Benzenesulfonic acid, C10-13-(linear) alkyl derivatives, calcium salt EC No 932-231-6, CAS# 1335202-81-7				
Skin Irrit.2	H315	Causes skin irritation	Warning	

Hazard class and category	Hazard statement code	Hazard statement	Signal word	Pictogram
Eye Dam. 1	H318	Causes serious eye damage	Danger	
Aquatic Chronic 3	H412	Harmful to aquatic life with long lasting effects	No signal word	No pictogram
2-Ethylhexan-1-ol CAS# 104-76-7				
Skin Irrit. 2	H315	Causes skin irritation	Warning	
Eye Irrit.2	H319	Causes serious eye irritation		
Acute Tox. 4	H332	Harmful if inhaled		
STOT SE 3	H335	May cause respiratory irritation		
Aquatic Chronic 3	H412	Harmful to aquatic life with long lasting effects	No signal word	No pictogram
Emamectin benzoate CAS# 155569-91-8				
Acute Tox.3	H301	Toxic if swallowed	Danger	
Acute Tox. 3	H311	Toxic in contact with skin		
Acute Tox. 3	H331	Toxic if inhaled		
Eye Dam. 1	H318	Causes serious eye damage	Danger	
STOT SE 1	H370	Causes damage to organs	Danger	
STOT RE 1	H372	Causes damage to organs through prolonged or repeated exposure		
Aquatic Acute 1	H400	Very toxic to aquatic life	Warning	
Aquatic Chronic 1	H410	Very toxic to aquatic life with ling lasting effects		
2,6-Di-tert-butyl-p-cresol CAS# 128-37-0				
Aquatic Chronic 1	H410	Very toxic to aquatic life with ling lasting effects	Warning	

4.3 Study focus: GHS classification of N-methyl-2-pyrrolidone

	As indicated in Table 4.2.1, NMP is classified as Repr. 1B and falls in one of the CMR categories that the Registrar intends to prohibit, as explained in Section 1 of this report. **Repr. 1B Presumed human reproductive toxicants - largely based on animal studies.** • Clear evidence of adverse effects on sexual function and fertility or on development in absence of other toxic effects has been identified; or • If occurring with other toxic effects, the reproductive toxicity effect is not considered to be a second non-specific consequence of the other toxic effects.

5 Environmental fate assessment

5.1 Summary

Physical/chemical properties and environmental fate aspects of NMP are summarised in Table 5.1.1. Unit conversions were done for vapour pressure and Henry's law constant.

Table 5.1.1: Physical/chemical properties of NMP that determine its environmental fate.

Property	Value	References
Selected physical/chemical parameters		
Molecular weight (g/mol)	99.1	USEPA 2018
Solubility in water (g/litre, 25°C)	1 000	
Vapour pressure (Pa, 25°C)	46.0	
Henry's law constant at 25°C ($Pa.m^3/mol$)	3.24E-04	
Octanol-water partition coefficient (Log K_{OW}),	-0.38	
Behaviour in air		
Photodegradation half-life (hours)	5.8	USEPA 2015(a)
Persistence in water		
Hydrolysis half-life	Does not undergo hydrolysis	
Biodegradation	73% in 28 days (aerobic in water) Readily/inherently biodegradable according to various OECD test protocols	
Mobility in soil		
Biodegradation half-life	4 days in a clay soil 8.7 days in a loam soil 11.5 days in a sandy soil	USEPA 2015(a)
Log K_{OC}	0.9	
Bioconcentration and bioaccumulation		
Bioaccumulation factor (BAF)	0.9 (estimated)	USEPA 2015(a)
Bioconcentration factor (BCF)	3.16	

5.2 Environmental fate descriptions

If NMP is released into the atmosphere, it is expected to remain solely in the vapour-phase, based on its vapour pressure. Neat NMP is slightly volatile, considering its vapour pressure (46 Pa). Substances with vapour pressure above about 10 Pa at 20 °C are considered volatile. The rate of volatilisation from water is expected to be low, based on a Henry's Law constant of 3.24E-04 $Pa.m^3/mol$. Generally, substances with Henry's law constant <1 Pa m^3/mol can be considered non-volatile. NMP is thus not removed from water through volatilisation.

Vapour-phase NMP degrades in air through reaction with photochemically produced hydroxyl radicals. The half-life of this reaction is approximately 5.8 hrs. NMP in the atmosphere would dissolve into water droplets, from where it will be removed by condensation or further reactions with hydroxyl radicals.

When released into water, NMP is not expected to adsorb to suspended solids or sediment in the water column, based upon low soil organic carbon partitioning coefficient (log K_{oc} = 0.9). There would thus be insignificant removal of NMP from water through sorption onto sediments.

NMP is expected to display high mobility in soil. It may volatilise from soil surfaces, or migrate downwards through soil and contaminate groundwater. NMP has high water solubility.

Several studies were conducted on human and environmental health risks associated with industrial use of NMP, but these reports did not identify possible degradation products, and did not indicate that degradation products could be more hazardous than NMP (WHO 2001, Environment Canada, Health Canada 2017; USEPA 2015(a); USEPA 2018). These are authoritative agencies, and it should be concluded that health risk assessments conducted for NMP would represent the upper limit of risk, covering also potential risks due to degradation products.

USEPA (2015a) estimated a bioaccumulation factor ("BAF") and a bioconcentration factor ("BCF") of 0.9 and 3.16, respectively, indicate that bioaccumulation and bioconcentration in aquatic organisms would be low. USEPA (2015a) reported that biodegradation studies have consistently shown NMP to be readily biodegradable, as summarised in Table 5.1.1. Overall, NMP can be expected to have low bioaccumulation potential and low persistence.

6 Pesticide action and benefits assessment

WARLOCK® 19.2 EC is an emulsifiable concentrate insecticide with stomach action for the control of pests on apples and pears, citrus, groundnuts, maize and sweetcorn, pomegranates, stone fruit, sunflowers, tomatoes, table and wine grapes. The active ingredient is emamectin benzoate (avermectin), with health and environmental hazards as listed in Table 4.2.1.

NMP is mainly used as a solvent for extraction in the petrochemical industry, as a reactive medium in polymeric and non-polymeric chemical reactions, as a remover of graffiti, as a paint stripper in the occupational setting, and for stripping and cleaning applications in the microelectronics fabrication industry. It is also used as a formulating agent in pigments, dyes and inks, and in insecticides, insecticides and fungicides. NMP is further used as an intermediate in the pharmaceutical industry, and to enhance the absorption of topically applied drugs. NMP is used as a solvent and a surfactant in cosmetic products. There are no known natural sources of NMP.

It has various attractive physical-chemical attributes, e.g., a high flash point compared to similar solvents. The boiling point is high, the freezing point is low, and handling is easy. It is chemically and thermally stable, miscible with water, and not corrosive to equipment.

7 The health risk assessment paradigm

A significant factor in the Organisation for Economic Co-operation and Development (OECD 2021) guidance document on key considerations for the identification and selection of safer chemical alternatives deals with the likelihood of exposure (human and ecological). OECD recommended that routes of exposure to a hazardous chemical that are unlikely, based on measured exposure data or physical-chemical properties of the substance of concern, should be excluded from the assessment. More correctly, the statement should refer to pathways of exposure (air, soil, water, and sediment), and routes of exposure (inhalation, ingestion, and dermal contact).

This recommendation of the OECD (2021) takes the assessment a step further from the hazard data of chemicals represented in the GHS, to the level where the potential for exposure of humans and ecological receptors is assessed, and through accounting for the toxicology of a substance or formulation, the level of risk is determined. This is aligned with the observations and recommendations of Karamertzanis et al. (2019).

Karamertzanis et al. (2019) evaluated the impact on classifications of carcinogenicity, mutagenicity, reproductive and specific target organ toxicity after repeated exposure in the first ten years of implementation of the REACH[1] regulation. The authors highlighted that classification for carcinogenicity, mutagenicity, reproductive toxicity, and specific target organ toxicity (repeated exposure) ("STOT RE") triggers several obligations for manufacturers, importers, and professional users.

Karamertzanis et al. (2019) then stated:
"*In addition to such consequences under other legislations* (sic)*, registrants are required to carry out exposure assessment and risk characterisation for substances that are classified and, hence, classification under REACH is a trigger for risk assessment for human health."*

OECD (2021) referred to the European Centre for Ecotoxicology and Toxicology of Chemical's ("ECETOC")[2] Targeted Risk Assessment ("TRA") tool for calculating the risk of exposure from chemicals to workers, consumers, and the environment. This illustrates the logic of basing the final decision about the safety of a chemical or formulation on health risk assessment, rather than only on hazard identification, as represented in the GHS.

The original paradigm for regulatory human health risk assessment ("HHRA") in the USA was developed by the US National Research Council (NRC 1983). This model has been adopted and refined by the US Environmental Protection Agency ("USEPA") and other international agencies as published under the International Programme on Chemical Safety (IPCS 1999; IPCS 2010), and is widely used for quantitative human health risk assessments.

Figure 7.1 illustrates the health risk assessment paradigm in a simple diagram.

[1] Registration, Evaluation, Authorisation and Restriction of Chemicals.
[2] http://www.ecetoc.org/tools/targeted-risk-assessment-tra/.

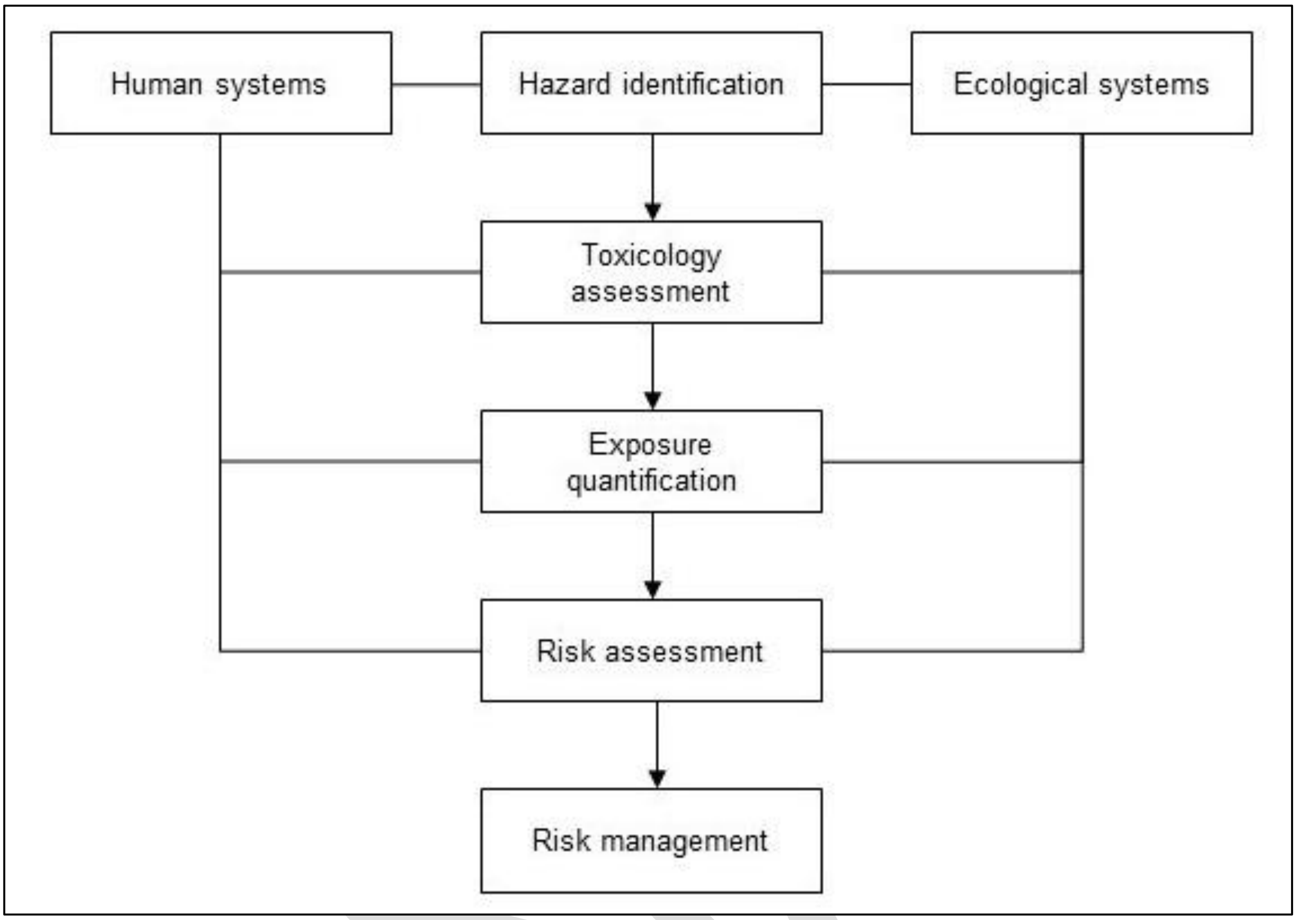


Figure 7.1: The holistic health risk assessment paradigm.

It is shown in this INFOTOX report that exposure assessment and health risk quantification are essential steps in managing health risks associated with hazardous chemicals.

8 Human health risk assessment methodology

The human health risk assessment ("HHRA") paradigm divides human health risk assessment into several logical steps, as illustrated in Figure 7.1. All of these are not fully applicable to the generic toxicological risk assessment for the purpose of derogation:

- **Hazard assessment** is the identification of the chemical constituent of concern and the hazard it poses, in this case reproductive/developmental toxicity hazards of NMP. This is discussed in Section 9.3.2.

- **Dose-response assessment** (toxicological assessment) addresses the relationship between levels of uptake and the manifestation of adverse effects (reproductive/developmental toxicity).

    - Toxicological information from available reproductive/developmental studies and applied standard risk assessment methodologies are used to derive a point of departure ("POD") or acceptable exposure level ("AEL"), and a level of concern ("LOC") for the HHRA purposes, by applying appropriate uncertainty factors and safety factors for infants and children, referring to dose through the routes of exposure. The derived toxicological values will be protective specifically against potential reproductive/developmental effects of the product. This ensures compliance with the Guideline for the Application for a Derogation for an

Agricultural Remedy Identified as a Substance of Concern, issued by the registrar: Act 36 of 1947, in February 2024. Health risks are assessed following the margin of exposure ("MOE") approach. The MOE approach is basically a comparison of the calculated exposure dose and the toxicity limit value for a specific health effect, referred to as the health effect endpoint.

  - The calculated MOE is compared to the level of concern ("LOC"), also referred to as a benchmark MOE. The LOC is the margin of exposure between the calculated exposure and the POD that indicates a risk of health effects associated with the calculated exposure. Each POD is associated with a specific numerical LOC value. Therefore, if a calculated MOE is higher in value than the LOC associated with the POD used for the MOE calculation, a risk to health under the assessed exposure conditions is highly unlikely and excluded for all practical purposes. However, if the calculated MOE is lower than the associated LOC, a risk to health cannot be excluded.

- **Exposure assessment considers** the identification of environmental pathways, potentially exposed groups, routes of direct and indirect exposure, and estimates of concentrations and duration of exposure. A conceptual model/matrix of application practices and exposure pathways and routes applicable to the identified receptors was constructed to guide the exposure assessment for the health risk assessment.

  The HHRA focuses on the following occupational exposure scenarios:
  - The oral, dermal and inhalation routes of exposure of pesticide mixers and applicators.
  - The dermal and inhalation post-application exposure of workers re-entering treated fields.

  Residential exposure scenarios are not assessed in terms of crop application or post-application scenarios, because the pesticide is not for sale in retail outlets catering to the general public. Therefore, potential spray drift in non-occupational settings, which may result in exposures of adults and children to NMP, need not be considered.

  INFOTOX covers all these scenarios in the health risk assessment, referring to published risk assessment studies.

  The primary information presented in the derogation document is the exposure factors applicable to the occupational scenario (mixers, applicators and other crop workers), and post-application exposure of members of the public.

- **Risk characterisation** involves the integration of the components described above. The risk characterisation also provides a review of documented human exposure incidents, if available.

- **Uncertainty review** identifies the nature and, when possible, the magnitude of the uncertainty and variability inherent in the characterisation of risks.

9 Toxicological review

9.1 Absorption by routes of exposure

NMP is readily absorbed by all routes of exposure. Due to its low vapour pressure, absorption through the skin represents the most likely and potentially the most significant route of exposure under most known consumer use conditions (WHO 2001).

The percutaneous absorption of NMP differs when NMP is applied as pure NMP or as an NMP solution. It should be considered that dermal absorption was evaluated primarily for industrial uses of NMP, such as paint stripping, where the neat product is used. In a dermal absorption study in the rat, the absorbed amounts of applications of pure NMP, and 30 per cent NMP in water, were 31 per cent and 3.5 per cent, respectively (Huntington Life Sciences 1998, cited in EC (2011) and WHO (2001)).

The NMP concentration in WARLOCK® 19.2 EC ranges from 10 to 30 per cent (Table 3.1); therefore, dermal absorption of 5 per cent is assumed. Where applicable, inhalation absorption of 100 per cent is assumed.

9.2 Acute toxicity

9.2.1 Oral exposure

NMP was shown to have low acute toxicity in animal tests. In a study with male and female Sprague-Dawley ("SD") rats, the LD_{50} was 4 150 mg/kg bw. Observed sub-lethal effects included ataxia and diuresis. The mouse oral LD_{50} value was 7 725 mg/kg bw (OECD 2009).

9.2.2 Dermal exposure

NMP exhibited low acute toxicity in SD rats, with the undiluted test substance applied to the shaved skin under an occlusive dressing for 24 hours, followed by a 14-days observation period and gross pathology examination. The LD_{50} value was > 5 000 mg/kg bw. Female Wistar rats also showed no mortality at 5 000 mg/kg bw, but all animals died at 10 000 mg/kg bw and the calculated LD_{50} value was 7 000 mg/kg bw (OECD 2009).

9.2.3 Inhalation exposure

The acute inhalation toxicity of NMP was investigated at a single concentration of 5.1 mg/litre in a group of 5 male, 5 female Wistar rats with 4-hours head-nose exposure of a vapor/aerosol mixture, followed by an observation period of 14 days. Weight gains were observed, but no mortalities; interpreted as indications of low acute toxicity. The estimated LC_{50} is > 5.1 mg/litre (OECD 2009).

9.3 Repeated-exposure toxicity

9.3.1 The USEPA systematic literature review

The USEPA (2020) conducted a systematic literature search. Inclusion and exclusion criteria were applied to title and abstract screening of the initial literature search results, comprising of 1 397 entries. Of these, 1 361 were excluded based on the criteria established for populations, exposures, comparisons, and outcomes ("PECO"). In addition, seven key/supporting studies were identified in addition to this process and included in the evaluation. The remaining 40 studies were evaluated using data quality evaluation criteria and acceptable hazard data then extracted and integrated.

INFOTOX did not repeat this robust USEPA systematic literature review. The information contained in the scientific publications that were found acceptable was used in the INFOTOX health risk assessment of NMP. The source documents are referenced in this INFOTOX report.

9.3.2 Developmental toxicity

The systematic literature search confirmed that there is robust evidence of developmental toxicity in animals exposed to NMP. Inhalation, oral and dermal exposures to NMP have been linked to a range of developmental effects, including decreased foetal and pup weights, and increased embryo/foetal and pup mortality (USEPA 2020).

Reproductive toxicity endpoints have been identified following repeated exposures to NMP, including reduced male fertility and female fecundity, and testicular histopathology. However, the USEPA (2020) concluded that evidence of reproductive toxicity is inconsistent across studies.

9.3.3 Neurotoxicity

The USEPA (2020) mentions two cross-sectional human occupational studies of a range of neurological endpoints that did not show significant associations between NMP exposure and neurological endpoints, but very small sample sizes and limitations in study design (including reliance on self-reported effects for some endpoints) constrains the conclusions that can be made.

Animal studies are available, with the following results, all reviewed by the USEPA (2020):

- A 90-day oral repeated-dose study in rats with a decreased body weight NOAEL of 169 and 217 mg/kg-day for males and females, respectively, and reversible neurological effects (including increased foot splay and low arousal) in males.
- A four-week rat study, with whole body aerosol exposure to 0.1, 0.5, and 1.0 mg/litre, 6 hours/day, five times a week, producing lethargy and irregular respiration at all concentrations. These signs were reversible within 30 to 45 minutes following cessation of exposure at the two lower concentrations. The study is not useful for point-of-departure (benchmark) determination, since actual exposure concentrations cannot be determined due to aerosol formation and condensation.
- In a gestational study with NMP aerosol concentrations (determined analytical) of 100 and 360 mg/m^3 for 6 hours/day the exposed dams exhibited sporadic lethargy and irregular respiration during the first three days of exposure, but not during the remainder of the exposure period or during the 10-day recovery period.

9.3.4 Carcinogenicity and endocrine disruption

The USEPA (2020) concluded that the available animal studies do not provide strong evidence for carcinogenicity and are insufficient to support a quantitative NMP cancer risk characterization for inhalation and dermal exposures:

- A suitable oral dietary exposure study in rats found no significant increase in tumour incidence, while the mice study reported a small but significant increase in liver tumour incidence in males only, in the high dose group.

- In a suitable inhalation study, inconclusive evidence of pituitary adenocarcinomas was observed.

The USEPA (2020) did not find sufficient information to evaluate potential endocrine disruptive activities.

9.4 Toxicity values for risk assessment

The USEPA (2020) concluded that the best representative endpoints for non-cancer effects were from acute (reproductive toxicity) and chronic (developmental toxicity) inhalation and dermal exposures for all conditions of use.

Acute exposures health risks to workers, occupational non-users, consumers, or bystanders from consumer use, were evaluated by the USEPA based on developmental toxicity endpoint values obtained from animal studies. The toxicity endpoint is post-implantation loss, assessed in terms of foetal resorptions and foetal mortality. The use of a developmental toxicity endpoint for the acute exposure POD raises the question of temporal windows of vulnerability to a toxic effect, and whether acute exposures (at levels not overtly toxic to the mother) can produce a permanent adverse effect on human development. The USEPA (2020) concluded that the reasonably available literature suggests the possibility, and accepted the NMP post-implantation loss endpoint as applicable to acute exposures. Foetal mortality represents the most severe endpoint associated with the developmental hazard profile for NMP.

The relevant oral (Saillenfait et al. 2002) and inhalation (Saillenfait et al. 2003) study data are presented in Table 9.4.1. The USEPA (2020) did not derive a POD for dermal exposure. In the absence of a dermal POD, it is customary to use the oral POD to assess dermal exposure risks, with application of the dermal absorption factor (of 5 per cent, see Section 9.1) to extrapolate exposure calculations from the oral route to the dermal route.

For chronic exposures, the USEPA based the risk determination on observed reproductive toxicity (decreased male fertility) endpoints. Reduced fertility in males is the most sensitive effect associated with chronic exposures. Risk determinations based on this sensitive endpoint are expected to be protective of other less sensitive non-cancer effects (*e.g.,* liver toxicity, kidney toxicity, immunotoxicity, neurotoxicity, irritation and sensitization). The chronic POD based on effects on reduced male fertility is supported by effects on female fecundity and developmental toxicity in a similar dose range (USEPA 2020).

Chronic exposure is not an important scenario relevant to occupational insecticide spray applications of WARLOCK® 19.2 EC on crops, because pest control strategies involve discrete spraying events, according to the label instructions. Label instructions stipulate spraying at the first signs of pest presence. Application may be repeated if necessary, applying at intervals of 7 to 10 days, but a maximum of 4, but often 2 times, per growing season. The USEPA (2015a) had concluded that, since NMP is rapidly metabolized and excreted, it is considered unlikely that more frequent use (*e.g.*, repeated weekly use of paint strippers) will result in risks, provided that the single-use scenarios had an adequate MOE. This approach fits with the proposed pesticide application strategy. Furthermore, the USEPA (2015a) concluded that, "*given the half-life ($t_{1/2}$) is approximately 2.5 hrs, exposures are effectively independent events*", unless multiple projects are undertaken over a very short time, which is not applicable to the WARLOCK® 19.2 EC application scenario.

The USEPA (2020) did not derive a short-term (1 to 30 days) POD, but used only acute- and chronic-exposure PODs for the risk assessment. An explicit explanation for this omission was not given, although implied reasons may be that the developmental toxicity studies used to derive acute PODs involved repeated exposures for 14 days (GD 6 to 20) in any case. In addition, the above (USEPA 2015a) conclusion that repeated exposures are effectively independent events is also relevant to the short-term exposure scenario. Therefore, the assessment of acute exposures effectively also covers the short-term exposure scenario, and a short-term POD is not critical for the purposes of the WARLOCK® 19.2 EC assessment.

The studies from which the acute endpoints were obtained are presented in Table 9.4.1. The USEPA used physiologically based pharmacokinetic (“PBPK”) modelling to derive the internal NMP blood concentrations of the study animals at the chosen PODs. The internal blood concentrations of the study animals where then compared with the human internal dose estimates, also determined by PBPK modelling, based on multiple route exposures measured or modelled in various NMP use scenarios. Internal dose estimates were compared using the MOE approach (see Section 8).

PBPK modelling will not be the method used to determine human exposures in this report. The USEPA (2020) exposure scenarios for PBPK modelling are not aligned with the use of NMP as a non-active ingredient in an insecticide application, relevant to WARLOCK® 19.2 EC. Insecticide applications are assessed according to the recommendations of the Technical Notes for Guidance (“TNsG”) on Human Exposure to Biocidal Products, compiled by the European Chemicals Bureau (“ECB”) of the European Commission (“EC”) (ECB 2002). The TNsG provides indicative exposure values for a range of generic exposure scenarios discussed in the TNsG, amongst these occupational exposure in agricultural application scenarios. The calculations for NMP exposure due to application of WARLOCK® 19.2 EC are done according to the TNsG examples, following the MOE approach. For this purpose, exposure dose (not the internal dose) PODs are required, and these are summarised from the USEPA (2020) in Table 9.4.1.

Table 9.4.1: Summary of NMP acute exposure reproductive and developmental effects.

*Point of departure (POD)	Uncertainty Factors	Level of concern	**Study and toxicological effects
Acute - developmental effects			
NOAEL = 125 mg/kg-day	UF_A= 3 UF_H= 10 Total UF= 30	LOC = 30	<u>Oral</u> gavage (0, 125, 250, 500, 750 mg/kg-day) on gestational days (“GD”) 6 to 20 in rats (Saillenfait et al. 2002). Effects: • Increased resorptions/ post-implantation losses. • Increased skeletal malformations. • Decreased foetal body weights; NOAEL for developmental effects = 125 mg/kg-day • NOAEL for maternal toxicity = 250 mg/kg-day
NOAEL = 243 mg/m^3	UF_A= 3 UF_H= 10 Total UF= 30	LOC = 30	<u>Inhalation</u> exposure (0, 122, 243, 487 mg/m^3); 6 hours/day on GD 6 to 20 in rats (Saillenfait et al. 2003). Effects: • Reduced maternal weight gain and food consumption at 243 mg/m^3. • NOAEL for maternal effects = 122 mg/m^3. • Reduced foetal weight at 487 mg/m^3 exposure. • NOAEL for developmental effects = 243 mg/m^3.
HEC dose = 48 mg/kg-day	Assuming UF_A was not applied in the HEC calculation, the total UF and the LOC remains 30, as above.		<u>Inhalation</u> dose, calculated by Kirman et al. (2023) from the NOAEL of 243 mg/m^3 (Saillenfait et al. 2003).

**Source: USEPA (2020).
*Point of Departure (POD): Data point derived from dose-response data, used to extrapolate risks associated with lower environmentally relevant human exposures. NOAEL: no-observed-adverse-effect level. LOAEL: lowest-observed-adverse-effect level. UF: uncertainty factor. UFA: extrapolation from animal to human (interspecies). UFH: potential variation in sensitivity among members of the human population (intraspecies). LOC: level of concern. HEC: human equivalent concentration.

10 Human dietary risk assessment

NMP is used in many industries as a solvent for cleaning or degreasing, paint stripping, and multiple uses in product manufacturing processes. NMP is also used as a solvent/cosolvent in pesticide products for agricultural use, which is relevant in the assessment of WARLOCK® 19.2 EC. The risk assessment documentation consulted for this INFOTOX assessment deals primarily with industrial uses of NMP, and its presence in industrial and consumer products.

NMP is currently approved in the USA for use as a solvent and co-solvent inert ingredient in pesticide formulations for both food and non-food applications, and is exempt from the requirements of a tolerance limit, that is, a maximum allowable residue limit (40 CFR Part 180.920). These decisions considered developmental and reproductive effects of NMP. In 2006, the Registration Division of the Office of Chemical Safety and Pollution Prevention of the USEPA conducted a reassessment of the exemption, as required under the Food Quality Protection Act. It was concluded that the exemption was to be maintained (USEPA 2006) and subsequently confirmed in 2018 (USEPA 2018) and 2020 (USEPA 2020). This exemption infers reasonable certainty that no harm will result from aggregate exposures to the NMP pesticide residue associated with dietary exposure and all other non-occupational exposures. This conclusion is directly related to NMP's low acute toxicity (OECD 2009), and its physical/chemical and environmental fate properties, as described in Section 5. NMP is readily biodegradable and the bioaccumulation potential in biota is expected to be very low.

11 Human incident reports

INFOTOX could not find any reports on human incidents that occurred during handling of NMP, and potential health effects that were recorded during such incidents. Considering that NMP has low acute toxicity through all routes of exposure, as discussed in Section 9.2, and it has low persistence in environmental compartments, there is a low probability for significant human incidents resulting in significant health risks.

12 Ecological risk assessment

12.1 Aquatic and terrestrial organisms

The USEPA Office of Pollution Prevention and Toxics ("OPPT") did not include a quantitative assessment of environmental effects in its risk assessment (USEPA 2018). Because NMP has a low hazard profile for ecological receptors, and it exhibits low persistence and bioaccumulation if released into aquatic or terrestrial compartments, it is regarded as not necessary to conduct a health risk assessment for terrestrial receptors. Spray drift to non-target plants is not seen as potentially phytotoxic, considering that WARLOCK® 19.2 EC is applied directly onto crops.

USEPA (2018) conducted a literature search, of which the information is summarised in Table 12.1.1. Two studies were available on avian species, namely, a 14-day study on bobwhite quail (*Colinus virginianus)* with LD_{50} of 2 500 to 5 000 mg/kg bw, and an 8-day study on mallard duck (*Anas platyrhynchus*) with LD_{50} > 5 000 mg/kg bw (Hazelton 1980, cited in OECD 2009). Based on the USEPA's assessment criteria, NMP has low acute and chronic toxicity to aquatic organisms and birds.

A data quality evaluation was performed on the studies used to characterise the environmental hazards of NMP (USEPA 2020), which confirmed the study results confidence ratings as "high". This supports the conclusion that the hazard of NMP to aquatic organisms and birds is low, and that no further evaluation is required.

Table 12.1.1: Ecological hazard characterisation of NMP.

Duration	Test organism	Toxicity parameter	Value (mg/litre)	Effect endpoint	Reference
Aquatic organisms					
Acute	Fish	LC_{50}	>500-4 030	Mortality	BASF 1983; BASF 1986, cited in OECD 2009
	Invertebrates	EC_{50}	1.23-4 897	Immobilisation	Lan et al. 2004; GAF 1979, cited in OECD 2009
	Algae	EC_{50}	>500-600.5	Growth	ECHA 2014
Chronic	Fish	Extrapolated chronic toxicity value ("ChV")	>50	An acute to chronic ratio of 10 (divide by 10) was used to extrapolate a chronic toxicity value based on the lowest reported acute value (USEPA 2020).	
	Invertebrates	NOEC	12.7	Reproduction	BASF 2001, cited in OECD 2009
		LOEC	25		
		*ChV	7.68		
	Algae	NOEC	125		
Terrestrial organisms					
Acute	Avian	LD_{50}	2 500-5 000	Mortality	Hazelton 1980, cited in OECD 2009

* The ChV (chronic value) listed here is the geometric mean of the NOEC and the LOEC.

It is also useful to present the ecological risk characterisation of NMP by Environment Canada, Health Canada (2017), confirmed in 2024 (Environment and Climate Change Canada, Health Canada 2024). Ecological risk was characterised using the methodology for ecological risk classification of organic substances ("ERC"). ERC is a risk-based approach that considers multiple metrics for hazard and exposure, and weighting of evidence.

Hazard profiles are established based principally on mode of toxic action, chemical reactivity, food-web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity metrics. Exposure profile metrics include potential emission rate, overall persistence and long-range transport potential. A risk matrix of hazard and exposure profiles (summarised in Table 12.1.2) is used to assign a low, moderate or high level of potential concern for a substance. This approach reduces uncertainty in risk characterisation, since it includes far more data and information than a single metric-single medium approach (e.g., LC_{50}). The ERC assigned to NMP reflects a low-level potential to cause ecological harm. Environment and Climate Change Canada, Health Canada (2024) concluded that, *"(c)onsidering all available lines of evidence presented … there is low risk of harm to organisms and the broader integrity of the environment from NMP"*.

Table 12.1.2: Ecological risk classification of NMP.

ERC hazard classification	ERC exposure classification	ERC risk classification
Low	Low	Low

12.2 Honey bees

Shannon et al. (2023) conducted a review of the risks of spray adjuvants to honey bees. NMP, as an inert pyrrolidone emulsifier, is covered in the review article, and was found to be highly toxic to larval honey bees (Zhu et al. 2014, cited in Shannon et al. 2023).

The potential risk to honey bees is mitigated in the use restriction on the WARLOCK® 19.2 EC label: **"***Do not use WARLOCK® 19.2 EC during flowering and when bees are actively foraging, as the product can be toxic to bees***."**

13 Ecological incident reports

INFOTOX could not find any reports on ecological incidents that occurred during handling of NMP, or potential environmental effects that were recorded during such incidents. Considering that NMP has low acute toxicity to ecological receptors and low potential for persistence in environmental compartments, as discussed in Section 12, there is a low probability of incidents that might result in significant ecological risks.

14 Occupational exposure risk calculations

14.1 Exposure and risk equations

Exposure and risk equations commonly used for the assessment of agricultural occupational handlers/mixers/applicators and post-application re-entry workers are presented in this section. Occupational exposure is calculated in terms of the NMP exposure and concentrations.

<u>Occupational handler equations</u>

Potential daily exposures for handlers are calculated using the following formulas:

$$E = UE * AR * A * 0.001\ mg/ug$$

Equation 14.1.1

where:

E	exposure (mg NMP/day)
UE	unit exposure (µg NMP/kg NMP)
AR	maximum application rate according to proposed label (kg NMP/ha or kg NMP/litre)
A	area treated or amount handled (e.g., ha/day, litre/day)

The daily doses are calculated using the following formula:

$$ADD = \frac{E * AF}{BW}$$

Equation 14.1.2

where:

ADD	average daily dose absorbed in a given scenario (mg ai/kg-day)
E	exposure (mg ai/day)
AF	absorption factor (dermal and/or inhalation)
BW	body weight (kg)

Non-cancer risk estimates for each scenario are calculated using the Margin of Exposure (MOE) approach, which is a ratio of the POD to the daily dose of concern.

All MOE values are calculated using the following formula:

$$MOE = \frac{POD}{ADD}$$

Equation 14.1.3

where:

MOE	margin of exposure: value used by the USEPA to represent risk estimates (unitless)
POD	point of departure (mg/kg-day)
ADD	average daily dose absorbed in a given scenario (mg ai/kg-day)

Occupational post-application (re-entry) equations

Potential daily exposures for occupational post-application workers are calculated by the USEPA (2016) using the following formulas with empirical measurement units:

$$DFR_t = AR * F * (1-D)^t * \left(4.54E8 \frac{ug}{lb}\right) * \left(2.47E\text{-}8 \frac{A}{cm^2}\right)$$

Equation 14.1.4

where:

DFR_t	dislodgeable foliar residue on day "t" (µg/cm^2)
AR	application rate (lb NMP/A)
F	fraction of NMP retained on foliage, or default of 25% (unitless)
D	fraction of residue that dissipates daily, or default of 10% (unitless)
T	number of days after application day (days)

Metric measurement units are used in South Africa, in which case the equation is adjusted as follows:

$$DFR_t = AR * F * (1-D)^t * (1E9\ \mu g/kg) * (1E\text{-}8\ ha/cm^2)$$

where:

DFR_t	dislodgeable foliar residue on day "t" (µg/cm^2)
AR	application rate (kg NMP/ha)
F	fraction of NMP retained on foliage, or default of 25% (unitless)
D	fraction of residue that dissipates daily, or default of 10% (unitless)
T	number of days after application day (days)

$$E = TC * DFR_t * ET * 0.001 \frac{mg}{ug}$$

Equation 14.1.5

where:

E	exposure (mg ai/day)
TC	transfer coefficient (cm^2/hr)
DFR_t	dislodgeable foliar residue on day "t" (µg/cm^2)
ET	exposure time (hours/day)

The transfer coefficients (TCs) used for these calculations, and presented in Annexure 1, are based on standard clothing worn by agricultural field workers: shoes, socks, long-legged pants, and long-sleeved shirts. The TC associated with a specific activity, e.g., weeding or harvesting by hand, presents an estimate of the fraction of foliar residues (in this assessment, residues of NMP) transferred to the skin of re-entry workers during that activity. The TC is dependent on the crop type (foliage properties) and the specific activity undertaken in the treated crop.

The daily doses are calculated using the following formula:

$$ADD = \frac{E * AF}{BW}$$

Equation 14.1.6

where:

ADD	average daily dose absorbed in a given scenario (mg NMP/kg-day)
E	exposure (mg NMP/day)
AF	absorption factor (dermal and/or inhalation)
BW	body weight (kg)

The MOE is calculated with Equation 14.1.3. Dermal and inhalation MOEs are not added to obtain a combined MOE, because the toxic effect endpoints and PODs for the different routes of exposure are not the same (Table 9.4.1). Oral exposure effects include clear foetal malformations, which were not observed in the inhalation study.

14.2 Proposed WARLOCK® 19.2 EC use pattern and exposure profile

Crops and spray application methods

A summary of crops and spray application methods, provided on the WARLOCK® 19.2 EC label, is presented in Table 14.2.1, supplemented with technical information provided by the applicant (ADAMA South Africa (Pty) Ltd). According to the applicant, WARLOCK® 19.2 EC is only sold to commercial farmers and is not sold in the home and garden market. WARLOCK® 19.2 EC is not applied via aerial application, meaning a low-flying fixed-wing or rotary aircraft that applies spray in-flight, including from remotely-piloted aerial systems. It won't be applied with a handheld spray gun (attached to a hose, which is in turn attached, through a mechanical pressure pump, to a vehicle-mounted holding tank).

The usual practice is groundboom application, but it might, on rare occasions, be applied with a knapsack (backpack). Ground booms are mounted to a vehicle and applies spray downward from nozzles, attached to the spraying tank mounted on the same vehicle. This is a commonly-used crop application method. Backpack applications imply using a hand wand attached to a low-volume tank worn on a worker's back. While walking through the target area, the pesticide solution is sprayed by pressurising the spray tank, either by hand with a hand-pump, or mechanically with a small compressor pump attached to the backpack. These may be used for broadcast spraying, or for spot-spraying, which is the application of a pesticide only to specific, targeted areas where pests are present.

Table 14.2.1: WARLOCK® 19.2 EC crop and spray application matrix.

Crop	Market	Application method		Qualitative description of large-scale crop area
	Farming scale	Ground-boom	Backpack & handheld spray wand	
Fruits	**Large-scale**	✓	N.a.	Orchard
	Small-scale	N.a.	✓	N.a.
Groundnuts	**Large-scale**	✓	N.a.	Field crop, typical hectares
	Small-scale	N.a.	✓	N.a.
Maize and sweetcorn	**Large-scale**	✓	N.a.	Field crop, high hectares
	Small-scale	N.a.	✓	N.a.
Sunflower	**Large-scale**	✓	N.a.	Field crop, high hectares
	Small-scale	N.a.	✓	N.a.
Table and wine grapes	**Large-scale**	✓	N.a.	Vineyard
	Small-scale	N.a	✓	N.a.
Tomatoes	**Large-scale**	✓	N.a.	Field crop, typical hectares
	Small-scale	N.a	✓	N.a

Fruits: Citrus, pomegranates, stone fruit, pome fruit
N.a.: Not applicable

<u>Quantification of spray application according to spray equipment</u>

The small-scale use of backpacks is quantified in terms of the number of litres of solutions mixed, loaded into the backpack, and applied in one working day. The USEPA (2015b) studied exposure to workers during backpack and handgun application of liquid sprays in utilities rights-of-way, which is used in this report as an approximation of small-scale applications of WARLOCK® 19.2 EC. The reported spraying time with backpacks (USEPA 2015b) ranged from 2 to 10.7 hours, and the area sprayed from less than 1 to approximately 6 acres (less than 0.4 to 2.4 ha).

Two types of backpack sprayers are available in South Africa, namely, a backpack with a handheld sprayer, which is not mechanically-pressurized (Figure 14.2.1(a)), and a backpack with a mechanically-pressurized handgun sprayer, also referred to as a compressor sprayer, in which pressure is applied by a small motor mounted on the backpack (Figure 14.2.1(b)). The general volume of these backpack spray tanks is approximately 16 to 20 litres. The USEPA (2015b) observed that backpack workers sprayed 4.5 to 64.5 gallons (17 to 244 litres) of solution in 2 to 11 hours. The maximum volume was equivalent to 17 spray loads (17 tank volumes). Conservatively assuming that a small-scale farm pesticide applicator could handle 17 spray loads of 20 litres each during a work day, a conservative upper end estimate would be a total spray solution volume of 340 litres/day.

Groundboom spray application is quantified according to the label instructions, and the typical area treated, often determined by the crop type.

(b) Not mechanically pressurised (a) Mechanically pressurised

Source: Foqué (2012)

Figure 14.2.1: Backpack sprayers available in South Africa.

Quantification of area treated daily with groundboom, according to crop type

The areas to be treated (hectares) are the default areas presented in Table 14.2.2, according to the default area categories recommended by the USEPA Exposure Science Advisory Council Policy #9.1, or from other USEPA sources. The USEPA values are provided in acres (A) and converted to hectare (ha). A copy of the original Policy #9.1 could not be obtained, despite several attempts; therefore, the acreage values presented here are obtained from another USEPA Policy #15.2 (USEPA 2022), citing Policy #9.1, and are as used in multiple other pesticide exposure assessments by the USEPA.

Table 14.2.2: Area to be treated per day, according to crop types, groundboom application in large-scale farming.

Crop	Qualitative description of large-scale crop area	# Acres	Hectares
Fruits	Orchard	*40	16.2
Groundnuts	Field crop, typical hectares	80	32.4
Maize and sweetcorn	Field crop, high hectares	200	80.9
Sunflower	Field crop, high hectares	200	80.9
Table and wine grapes	Vineyard	*40	16.2
Tomatoes	Field crop, typical hectares	80	32.4
* The "area treated daily" for orchards and vineyards, using non-aerial application methods, which was used by the USEPA (2016) to calculate occupational exposures in a similar pesticide occupational exposure assessment.			

Personal Protective Equipment ("PPE")

PPE-use recommended on the product label includes protective gloves, protective clothing, eye protection and face protection. Respiratory protection is also recommended. Eye protection usually means tightly sealing safety goggles; protective gloves are usually water proof and prevents the bulk of chemical penetration, and suitable protective clothing usually means boots protecting against harmful chemicals, and a water repellent woven coverall.

For the purpose of the calculations presented here, use of the coverall is assumed, which is equivalent to the USEPA terminology “double-layered” clothing; [DL]. Since gloves [G] are recommended, the [DL/G] coding is applicable, as referred to in Table 14.4.1.1.

Respiratory protection is recommended on the WARLOCK® 19.2 label; therefore, the USEPA terminology code [R] for “respirator” is applicable. The coding is expanded according to the degree of inhalation exposure reduction, e.g., PF10 (90% reduction) or PF50 (98% reduction), as presented in Table 14.4.1.1.

Restricted-entry interval (“REI”)

REIs are not provided, but the label instructions specify entry after the spray deposit has dried, unless wearing protective clothing. An REI of 12 hours (0.5 days) is assumed.

Handler exposures

The term “handlers” describes those involved in the pesticide application process. Distinct job functions or tasks related to applications and exposures were identified by the USEPA, depending on the specifics of each task, such as:

- Job requirements (amount of chemical used in each application)
- Kinds of equipment used
- Treated target
- Level of protection used by a handler

The expected exposure scenarios and the quantitative exposure/risk assessment matrix developed for occupational handlers are presented in Section 14.3.

Post-application exposures

The term post-application is used to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests, moving irrigation pipes, or harvesting.

The occupational exposure profile is summarised in Table 14.2.3. The expected exposure scenarios and the quantitative exposure/risk assessment matrix developed for occupational post-application workers are presented in Section 14.3.

Occupational exposure profile

The occupational exposure profile is summarised in Table 14.2.3.

Oral exposure is excluded in both the handling (including application) and post-application scenarios:

- Occupational pesticide handlers are assumed to have sufficient training to follow label instructions:
    - Wash face, hands and any exposed skin thoroughly after handling.
    - Do not eat, drink or smoke when using this product.
    - NMP was shown to have low acute toxicity (Section 9.2.1).
- Post-application workers:
    - Hand-to-mouth activity during post-application activities should be negligible.

Inhalation exposure of post-application workers is considered negligible and is not assessed, because:

- Re-entry instructions are to enter only after applied product has dried off.
- NMP is slightly to reasonably volatile, since its vapour pressure (46 Pa at 25°C, Table 5.1.1) should be higher than 10 Pa at 20°C, the approximate value above which organic carbon substances are considered volatile.
- Therefore, a minimum of volatile foliar/crop residues should remain at the time of re-entry, and the minimal residue should be insufficient to pose a risk of inhalation exposure to post-application workers.

Table 14.2.3: Occupational exposure profile.

Type of worker	Exposure duration	Inhalation exposure	Dermal exposure	Oral exposure
Occupational pesticide handlers	Short-term (1 to 30 days)	✔	✔	N.a.
	Intermediate-term (1 to 6 months)	✔	✔	N.a.
Post-application workers	Short-term (1 to 30 days)	N.a.	✔	N.a.
	Intermediate-term (1 to 6 months)	N.a.	✔	N.a.

N.a: Not applicable

14.3 WARLOCK® 19.2 EC and NMP spray calculations

14.3.1 Background

The calculation of the spray application input values needed for the WARLOCK® 19.2 EC occupational exposure and risk calculations are presented in Tables 14.3.2.1 to 14.3.2.3, and in Table 14.3.3.1. Data are as obtained from the product label, and calculated based on the label directions for spray solution preparation.

Exposure calculations according to the USEPA equations described in Section 14.1 are presented in Section 14.4.

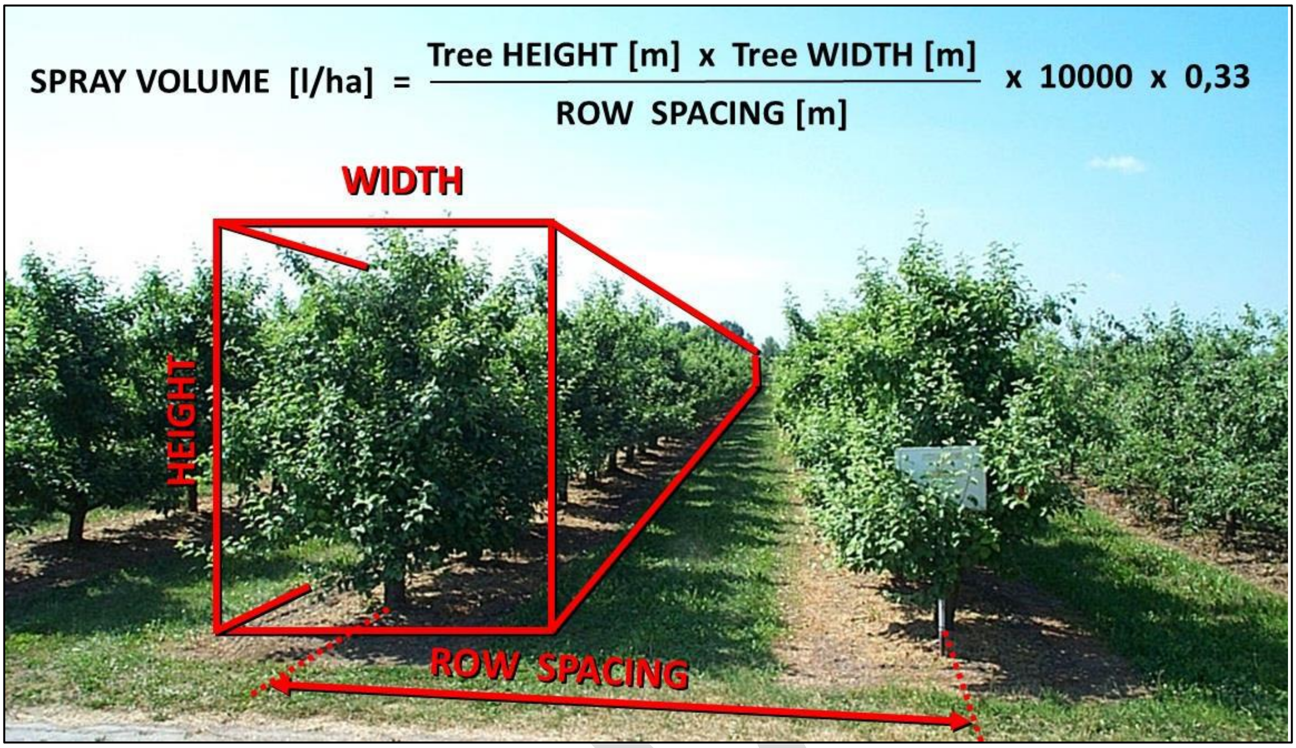
Post-application (re-entry) agricultural workers are exposed by the dermal route only, since oral and inhalation exposure is excluded, as motivated in Section 14.2 and presented in the occupational exposure profile (Table 14.2.3).

Completely mechanised application or post-application re-entry activities are highly unlikely to be associated with any significant exposure to workers and are not assessed.

14.3.2 Application rates for fruit trees and vines

<u>**The Unrath tree row volume (TRV)**</u>
The application instructions for fruits are somewhat different in that dosage rates are not provided directly per hectare, but the instruction is to "*Calculate the spray volume to be applied per hectare according to the tree-row-volume formula described by Unrath*". Dosage rates for table- and wine grapes are also not provided directly per hectare, but the instruction is to Apply WARLOCK® 19.2 EC as a full cover spray, ensuring thorough coverage. Dosage mixing instructions for fruits, table- and wine grapes are provided as volume product per volume water, as presented in Table 14.3.2.2, according to the product label.

The Tree Row Volume ("TRV") concept described by Unrath et al. (1986, cited in Sutton and Unrath 1988) is used to calculate the spray volume per hectare as illustrated in Figure 14.3.2.1.



Source: Doruchowski et al. (2012).

Figure 14.3.2.1: Tree Row Volume concept to determine spray volume.

In Figure 14.3.2.1:

- The factor "0.33" is the unit volume water, expressed as a volume of spray liquid per 1 m^3 of canopy volume, which is assumed to produce biologically efficacious spray coverage on the target (canopy foliage). For the orchards in Poland the unit volume is 0.33 litre/m^3, which has been tested during efficacy trials (Doruchowski et al. 2012).
- The factor "10 000" is the square meter per hectare adjustment factor (10 000 m^2/ha).

The original TRV calculation proposed by Unrath et al. (1986) is given in Equation 14.3.2.1.

$$TRV = \frac{Tree\ height \times Limb\ spread}{Cross{-}row\ spacing} \times 10\,000 \qquad \text{Equation 14.3.2.1.}$$

where:

TRV	Tree Row Volume (m^3 foliage/hectare)
Tree height	(m) as indicated in Figure 14.3.2.1
Limb spread	Tree width (m)
Cross-row spacing	Row spacing (m) as indicated in Figure 14.3.2.1
10 000	Square meter per hectare adjustment factor (m^2/ha)

Unrath et al. (1986) adjusted the TRV for foliar density on a scale from 0.7 to 1.0; 0.7 for extremely open trees with light penetration through the tree canopy and 1.0 for unpruned trees, with extremely dense foliage, with no light penetration. The factor 1.0 is used for the WARLOCK® 19.2 EC risk assessment, assuming a high-volume application on trees in full leaf (high leaf density), since trees are to be sprayed to run-off, requiring a higher spray volume. This is a conservative approach, ideal for the occupational health risk assessment.

The unit volume water per foliage volume
The final water volume per hectare is determined by multiplying the canopy-density-adjusted TRV by a fraction of 1 litre/7.48 m^3 (0.134 litre/m^3) for apples, since it was reported that 1 litre of water is sufficient to wet the foliage occupying 7.48 m^3 of canopy volume to the point of run-off (Unrath et al. 1986). The unit volume fraction of 0.134 litre/m^3 is assumed for all fruits (except grapes) in the WARLOCK® 19.2 EC risk assessment.

The unit volume factor used in this risk assessment for grape vines was obtained from Australian Wine Research Institute ("AWRI" 2010), which proposed a maximum factor of 45 to 75 litre per Unit Canopy Row ("UCR") for trellised vines in the vertical shoot position ("VSP" canopy). One UCR is defined as a 1-metre-wide and 1-metre-high canopy of 100 metre length, for spraying to run-off wetness. Therefore, one UCR equals a canopy volume of 100 m^3. The upper limit unit volume of 75 litre per 100 m^3 is equal to a value of 0.75 litre/m^3 (75 litre/100 m^3), which is used for the WARLOCK® 19.2 EC risk assessment on grapes with a full canopy. This is a conservative value, since the unit volume would be less for a "sparse" canopy.

Tree/vine dimensions for the TRV calculation
The default vine cross-row spacing used by AWRI is 3 metres, the upper value of the 2.1 to 3.0 m range proposed for South Africa (Vinpro online). A conservative median value of 2.6 m is used for this risk assessment. The typical row spacing for apples (assumed also for pears) in South Africa appears to be 4.5 m (Phillips 2013), but may be as low as 3.3 m in higher-yielding varieties in good quality soil (Mouton 2021); therefore, a median estimate of 3.9 m is assumed. The row width for citrus appears to be 6 m (Citrus Academy NPC 2017) and 5 m for pomegranates (Louw online (a)). Stone fruit spacing may depend on the type of fruit, but spacings of 3 x 3, 6 x 6, 4 x 4 or 4 x 6 m are variously recommended, while the modern trend appears to be trellised systems with closer spacings of 2.5 to 3 meters between trees (Veens 2013, plantnet.com.au and thegardner.co.za). The median stone fruit orchard spacing of 4 x 4 metres is used for the WARLOCK® 19.2 EC risk assessment.

The plant widths are assumed to be the intra-row plant spacing for each crop, which is 1 to 1.5 m between vines (wine.co.za); the conservative value of 1.5 m will be used; 1.5 m for apples and pears, 3 m for citrus, 2 m for pomegranates and 3.6 m for stone fruit (previous references).

The AWRI (2010) VSP vine canopy height corresponding to a unit volume factor of 45 to 75 litre per UCR is 2 m, which is used for the WARLOCK® 19.2 EC risk assessment. The tree heights assumed for apples and pears is 4 m, based on a range of "*1.8 to 4.6 m tall in cultivation*" (greencloudsolutions.co.za), and a height of 3 m being referred to as "*smaller trees*" (greenagri.org.za). Referenced citrus tree heights are 1 to 4 m (Stander 2015), the higher value of 4 m is used for calculations, and 2 to 2.5 m (Louw online (b)) for pomegranates, of which 2.5 m is used for the risk assessment. A standard value for stone fruits was not found, but a height of 4 m is used, the general higher value referenced for other fruit trees.

The dimensions presented in this section are used to calculate the TRV with Equation 14.3.2.1.

Spray volume calculations for WARLOCK® 19.2 EC
Spray volume calculations for the WARLOCK® 19.2 EC risk assessment are presented in Table 14.3.2.1. The calculated TRVs (Equation 14.3.2.1) are multiplied with the "unit volume water per foliage volume" to derive the spray volume. The canopy adjustment factor applied to all TRVs is 1.0, conservatively assuming a dense foliage canopy.

Table 14.3.2.1: Spray volume calculations for fruits.

Fruit	Tree height (m)	Limb spread (m)	Cross-row spacing (m)	TRV (m^3/hectare)	Unit volume fraction (litre/m^3)	Spray volume (litre/ha)
Vines: table and wine grapes	2	1.5	2.6	11 538	0.75	8 654
Apples and pears	4	1.5	3.9	15 385	0.134	2 062
Citrus	4	3	6	20 000	0.134	2 680
Pomegranates	2.5	2	5	10 000	0.134	1 340
Stone fruit	4	3.6	4	36 000	0.134	4 824

TRV (m^3/hectare) = (Tree height (m) × Limb spread (m)) / (Cross-row spacing (m)) × 10 000 (m^2/hectare) (Equation 14.3.2.1.).
Spray volume (litre/ha) = TRV (m^3/hectare) × Unit volume fraction (litre/m^3).

<u>**Product and NMP application rate calculations**</u>

The spray volume calculated in Table 14.3.2.1 and the product mixing instructions for fruits, provided on the WARLOCK® 19.2 EC label, are used to calculate the product and NMP application rates as presented in Table 14.3.2.2.

The upper limit percentage by weight of NMP in WARLOCK® 19.2 EC is 30 per cent (Table 3.1). The density of WARLOCK® 19.2 EC is not listed in the product SDS; therefore, a density of 1 g/ml is assumed. The converted concentration of NMP in WARLOCK® 19.2 EC is thus 300 g/litre (0.3 kg/litre) (Table 14.3.2.2). This is a conservative assumption, since the concentration could also be as little as 0.1 kg/litre (range of 10 to 30 per cent NMP in WARLOCK® 19.2 EC, Tabe 3.1).

The WARLOCK® 19.2 EC label stipulates the spray concentrations per 100 litre water as presented in Table 14.3.2.2, which is used to calculate the NMP concentration applied per hectare of crop.

The NMP concentration in the spray mix is also calculated, as this is an exposure parameter for the occupational pesticide handler (applicator) exposure assessment (Table 14.3.2.3).

Table 14.3.2.2: Product and NMP application rate calculations for fruits.

Fruit	Product concentration in spray water		Label: NMP concentration in product (kg NMP/litre)	**Spray volume (litre/ha)	***Calculated maximum kg NMP/ha
	Label: ml/100 litre water	*Converted: litre product/ litre water			
Vines: table and wine grapes	80 – 100 (100 for calculations)	0.001	0.3	8 654	2.596
Apples and pears	60 – 100 (100 for calculations)	0.001	0.3	2 062	0.619
Citrus	80 – 100 (100 for calculations)	0.001	0.3	2 680	0.804
Pomegranates		0.001	0.3	1 340	0.402
Stone fruit		0.001	0.3	4 824	1.447

* Conversion: 100 ml product / 100 litre water = 1 ml product / litre water = 0.001 litre product / litre water
**Spray volume (litre/ha): Table 14.3.2.1.
***Calculated maximum kg NMP/ha = **A x B x C**.
IF **A** = Converted product concentration in spray water (litre product/litre water).
B = Converted (kg NMP)/(litre product).
C = Spray volume (litre water/ha).

Table 14.3.2.3: NMP concentrations in the spray mix applied to fruits.

Fruit	Product concentration in spray water		NMP concentration in product	*Calculated maximum mg NMP/litre spray solution
	Label: ml/100 litre water	Converted: litre product/ litre water	Label: kg NMP/litre product	
Vines: table and wine grapes	80 – 100 (100 for calculations)	0.001	0.3	300
Apples and pears	60 – 100 (100 for calculations)	0.001	0.3	300
Citrus	80 – 100 (100 for calculations)	0.001	0.3	300
Pomegranates		0.001	0.3	300
Stone fruit		0.001	0.3	300

Converted: litre product/ litre water from Table 14.3.2.2.
*Calculated maximum mg NMP/litre spray solution = **A x B x 10^6 mg/kg**
IF **A** = Converted product concentration in spray water (litre product/litre water).
B = NMP concentration in product (kg NMP)/(litre product).

14.3.3 Application rates for non-fruit crops

Application rates for non-fruit crops are according to the label, as presented and calculated in Table 14.3.3.1.

Table 14.3.3.1: Product and NMP application rate calculations for non-fruit crops.

Crop	Product application per hectare		NMP concentration in product	*Calculated maximum kg NMP/ha	Label: Maximum spray volume (litre/ha)	**Calculated concentration NMP in spray mix (mg/litre)
	Label: maximum ml product/ha	Converted litre product/ha	Label: kg NMP/litre			
Groundnuts	700	0.700	0.3	0.210	1 000	210
Maize and sweetcorn	625	0.625	0.3	0.188	1 000	188
Sunflower	700	0.700	0.3	0.210	1 000	210
Tomatoes	750	0.750	0.3	0.225	1 000	225

*Calculated maximum kg NMP/ha = **A x B**.
IF **A** = Converted litre product/hectare.
B = Label: kg NMP/litre product.
Calculated concentration NMP in spray mix (mg/litre) = **C / D x 10^6 mg/kg
IF **C** = *Calculated maximum kg NMP/ha.
D = Label: Maximum spray volume (litre/ha).

14.4 WARLOCK® 19.2 EC risk calculations

14.4.1 Default values for risk calculations

Unit exposure default values

Equation 14.1.1 (Section 14.1) requires unit exposure values to calculate the exposure of pesticide operators mixing/loading/spraying the product.

The “unit exposure" is the mass of pesticide ingredient exposure per unit mass of ingredient handled, in units of µg/kg NMP [(µg NMP exposed) per (kg ai handled)].

Unit exposures are provided for specific combinations of exposure scenario (activity, equipment, formulation, site, etc.), exposure route, and PPE levels.

Values presented here are from the updated “*Occupational Pesticide Handler Unit Exposure Surrogate Reference Table*” (USEPA 2021). Unit exposure values per kg NMP are assumed representative of the unit exposure to NMP per kg NMP handled. The USEPA values are provided as µg/lb ingredient handled, which are converted to µg/kg handled, by multiplication with factor 2.205 lb/kg.

Table 14.4.1.1: Unit exposure values for NMP exposure and risk calculations.

Spray parameters		**Route of exposure**			
		Dermal [DL/G]		**Inhalation [R/PF10]**	
		µg/lb	**µg/kg**	**µg/lb**	**µg/kg**
Groundboom broadcast spray	Mixing/loading liquid for groundboom application	29.1	64.2	0.022	0.048
	Applying spray with groundboom	12.6	27.8	0.034	0.075
Backpack spray	Mixing/loading/application	16 900	37 265	6.91	15.24

[DL/G] assumes double-layered clothing (densely woven coverall) with gloves.
[R/PF10] assumes a respirator filter reducing inhalation exposure by 90%; that is, 10% of the exposure had a filter not been used.
Backpack spray unit exposure values are for “nurseries, Christmas tree farms, wildlife management, rights-of-way, forestry, conifer plantations, landscaping (turf/plants/bushes/trees)”

<u>Summary of terms and values for calculations</u>

A summary of terms and values for the risk calculations is presented in Table 14.4.1.2.

Table 14.4.1.2: Summary of terms and values for calculations.

Term	**Term symbol**	**Units**	**Value**
Unit exposure	UE	µg/kg ingredient handled	Table 14.4.1.1
(Maximum) application rate	AR	kg/ha or kg litre	According to product label (Tables 14.3.2.2, 14.3.2.3 and 14.3.3.1)
Area treated or amount handled	A	ha/day or litre/day	Groundboom default values in Table 14.2.2; Backpack total spray solution = 340 litres/day (Section 14.2).
Absorption factor	AF	unitless	Dermal: 5% (Section 9.1) Inhalation: 100% (Section 9.1)
Adult body weight	BW	kg	80 (USEPA 2011)
Point of departure	POD	mg/kg-day	Table 9.4.1, for different routes of exposure
Fraction of ingredient retained on foliage	F	unitless	25%, default
Fraction of residue that dissipates daily	D	unitless	0.10 (10%, default)
Number of days after application day	T	days	*Restricted-entry interval (REI) recommended on label is assumed to be at least 12 hours (0.5 days)
Transfer coefficient	**TC	cm^2/hr	See Annexure 1

Term	Term symbol	Units	Value
Dislodgeable foliar residue on day "t"	DFRt	μg/cm^2	Equation 14.1.4
Exposure time	ET	hours/day	Assumed 8 hours (workday), but only one exposure event before complete dissipation of deposited pesticide.

* WARLOCK® 19.2 EC Label directions: *Do not enter treated area until spray deposit has dried, unless wearing protective clothing.*

**TC: based on standard clothing worn by agricultural field workers: shoes, socks, long-legged pants, and long-sleeved shirts.

14.4.2 Results of risk calculations

Results of risk calculations for occupational handler exposure to NMP in WARLOCK® 19.2 EC are presented in Table 14.4.2.1 for groundboom application and Table 14.4.2.2 for backpack application.

Results for post-application re-entry workers (groundboom and backpack application) are presented in Table 14.4.2.3. All re-entry activities involve manual labour, assumed to present a risk of dermal contact with spray residues on crops and foliage. Non-manual or mechanised activities, such as mechanised harvesting, does not present a risk of dermal contact, and are thus not assessed.

Results are discussed in Section 15.

Table 14.4.2.1: Groundboom application: occupational handler exposure and MOEs.

Crop	AR_{max} (kg NMP/ha)	Dermal exposure			Inhalation exposure		
		Dose (mg/kg-day)	LOC = 30		Dose (mg/kg-day)	LOC = 30	
			MOE	MOE > LOC?		MOE	MOE > LOC?
Mixer / loader: Liquid, groundboom, broadcast							
Vines: table and wine grapes	2.596	0.0017	74 000	Yes	0.00003	1 890 000	Yes
Apples and pears	0.619	0.0004	311 000	Yes	0.00001	7 940 000	Yes
Citrus	0.804	0.0005	239 000	Yes	0.00001	6 110 000	Yes
Pomegranates	0.402	0.0003	479 000	Yes	<0.00001	12 210 000	Yes
Stone fruit	1.447	0.0009	133 000	Yes	0.00001	3 390 000	Yes
Groundnuts	0.210	0.0003	458 000	Yes	<0.00001	11 690 000	Yes
Maize and sweetcorn	0.188	0.0006	205 000	Yes	0.00001	5 240 000	Yes
Sunflower	0.210	0.0007	183 000	Yes	0.00001	4 680 000	Yes
Tomatoes	0.225	0.0003	428 000	Yes	<0.00001	10 910 000	Yes
Applicator: Groundboom broadcast spray							
Vines: table and wine grapes	2.596	0.0007	171 000	Yes	0.00004	20 000	Yes
Apples and pears	0.619	0.0002	718 000	Yes	0.00001	82 000	Yes
Citrus	0.804	0.0002	553 000	Yes	0.00001	63 000	Yes
Pomegranates	0.402	0.0001	1 105 000	Yes	0.00001	126 000	Yes

Crop	AR_{max} (kg NMP/ha)	Dermal exposure			Inhalation exposure		
		Dose (mg/kg-day)	LOC = 30		Dose (mg/kg-day)	LOC = 30	
			MOE	MOE > LOC?		MOE	MOE > LOC?
Stone fruit	1.447	0.0004	307 000	Yes	0.00002	35 000	Yes
Groundnuts	0.210	0.0001	1 058 000	Yes	0.00001	121 000	Yes
Maize and sweetcorn	0.188	0.0003	475 000	Yes	0.00001	54 000	Yes
Sunflower	0.210	0.0003	424 000	Yes	0.00002	48 000	Yes
Tomatoes	0.225	0.0001	987 000	Yes	0.00001	113 000	Yes

Notes to table:
AR_{max} (kg NMP/ha) is the *Calculated maximum kg NMP/ha,* in Tables 14.3.2.2 and 14.3.3.1.

Table 14.4.2.2: Backpack application: occupational handler exposure and MOEs.

Crop	Spray solution concentration (kg NMP/litre solution)	Dermal exposure			Inhalation exposure		
		Dose (mg/kg-day)	LOC = 30		Dose (mg/kg-day)	LOC = 30	
			MOE	MOE > LOC?		MOE	MOE > LOC?
Mixer / loader / applicator: Liquid, backpack							
Vines: table and wine grapes	0.3000	2.376	53	Yes	0.01943	2 500	Yes
Apples and pears	0.3000	2.376	53	Yes	0.01943	2 500	Yes
Citrus	0.3000	2.376	53	Yes	0.01943	2 500	Yes
Pomegranates	0.3000	2.376	53	Yes	0.01943	2 500	Yes
Stone fruit	0.3000	2.376	53	Yes	0.01943	2 500	Yes
Groundnuts	0.0002	0.002	75 000	Yes	0.00001	3 530 000	Yes
Maize and sweetcorn	0.0002	0.001	84 000	Yes	0.00001	3 953 000	Yes
Sunflower	0.0002	0.002	75 000	Yes	0.00001	3 530 000	Yes
Tomatoes	0.0002	0.002	70 000	Yes	0.00001	3 294 000	Yes

Notes to table:
Spray solution concentration (kg NMP/litre solution) is the *Calculated maximum mg NMP/litre spray solution,* in Table 14.3.2.3 for fruits, and the *Calculated concentration NMP in spray mix (mg/litre)* in Table 14.3.3.1 for non-fruit crops, all converted to kg NMP/litre for the backpack exposure and risk calculations.

Table 14.4.2.3: Post-application exposure and risks of re-entry workers.

Activity	AR_{max} (kg NMP/ha)	Dermal			
		Dislodgeable foliar residue at time of entry (DFR_t) (µg/cm^2)	Dose (mg/kg-day)	LOC = 30	
				MOE	MOE > LOC?
***Vineyard**					
Grape, table/raisin/juice/wine					
Pruning/weeding by hand, scouting, propagating	2.60	6.16	0.020	272	Yes

Irrigation hand set	2.60	6.16	0.058	181	Yes
Transplanting	2.60	6.16	0.007	815	Yes
Grape, table/raisin					
Harvesting by hand, tying/training, leaf pulling	2.60	6.16	0.169	740	Yes
Grape, juice/wine					
Harvesting hand, tying/training, leaf pulling	2.60	6.16	0.311	400	Yes
Grape, table					
Girdling/turning	2.60	6.16	0.594	210	Yes
Apples and pears					
Thinning fruit	0.62	1.47	0.026	4 700	Yes
Harvesting by hand	0.62	1.47	0.010	12 200	Yes
Pruning by hand	0.62	1.47	0.004	29 400	Yes
Weeding by hand, propping, orchard maintenance	0.62	1.47	0.001	170 400	Yes
Pomegranates					
Harvesting by hand	0.40	0.95	0.007	18 700	Yes
Scouting, pruning by hand	0.40	0.95	0.003	45 200	Yes
Transplanting	0.40	0.95	0.001	114 000	Yes
Weeding by hand, orchard maintenance	0.40	0.95	<0.001	262 200	Yes
Stone fruit					
Thinning fruit	1.45	3.43	0.062	2 000	Yes
Harvesting by hand	1.45	3.43	0.024	5 200	Yes
Pruning by hand	1.45	3.43	0.010	12 600	Yes
Weeding by hand, propping, orchard maintenance	1.45	3.43	0.002	72 800	Yes
Groundnuts					
Irrigation hand set	0.21	0.50	0.005	26 400	Yes
Scouting	0.21	0.50	0.001	239 000	Yes
Weeding hand	0.21	0.50	<0.001	717 100	Yes
Maize					
Irrigation hand set	0.19	0.44	0.004	26 400	Yes
Scouting	0.19	0.44	0.002	239 000	Yes
Weeding by hand	0.19	0.44	<0.001	717 100	Yes
Sweetcorn					
Detasseling (by hand and mechanically-assisted)	0.19	0.44	0.020	6 400	Yes
Irrigation, hand set	0.19	0.44	0.004	29 600	Yes
Scouting	0.19	0.44	0.002	51 100	Yes
Weeding by hand	0.19	0.44	<0.001	803 100	Yes

Sunflower					
Scouting and bird control	0.21	0.50	<0.001	557 700	Yes
Harvesting, mechanical	0.21	0.50	None	No exposure	Not applicable
Tomatoes					
Irrigation, hand set	0.23	0.53	0.005	24 700	Yes
Harvesting by hand, Tying/Training,	0.23	0.53	0.003	42 600	Yes
Transplanting	0.23	0.53	0.001	203 700	Yes
Scouting	0.23	0.53	0.001	223 100	Yes
Weeding by hand	0.23	0.53	<0.001	669 300	Yes

Notes to table:
Vineard: Depending on the ultimate use of the grape crop, different vineyard activities are applicable in some cases.
AR_{max} (kg NMP/ha) is the *Calculated maximum kg NMP/ha,* in Tables 14.3.2.2 and 14.3.3.1.
Inhalation risk is not calculated, because inhalation exposure is likely to be negligible (see Section 14.2).

15 Discussion of WARLOCK® 19.2 EC risk results

15.1.1 Mixing/spraying/application

All MOEs discussed in this section were calculated with a toxicity value based on health effects that include possible reproductive effects. The toxicity value is referred to as the POD, discussed in Section 9.4, and for which values are presented in Table 9.4.1. Therefore, where health effects are discussed in this section, it includes reproductive effects, which are the CMR hazard of concern for WARLOCK® 19.2 EC, due to the presence of NMP in the product.

The comparison between MOEs and LOCs for occupational handlers mixing and loading WARLOCK® 19.2 EC for spraying with a groundboom indicate that the calculated NMP doses to which these operators are exposed are not associated with a risk to health (all MOEs exceed the LOC) (Table 14.4.2.1). Similarly, a risk to health is not indicated for applicators involved in groundboom broadcast spraying (Table 14.4.2.1).

Operators mixing, loading and spraying WARLOCK® 19.2 EC with the use of a backpack (Table 14.4.2.2) are exposed to levels of NMP not associated with a risk to health (MOEs more than the LOC for all types of crops).

15.1.2 Post-application exposure and risks

Post-application exposure and risks of re-entry workers are presented in Table 14.4.2.3. Different re-entry activities are applicable to different crop types, and, in the case of vineyards, the type of activity depends on the ultimate use of the harvested grapes. For example, only table grapes and girdled and/or turned. The same activity in two different types of grapes (table or wine) may also have different transfer coefficients (TCs, presented in Annexure 1, discussed in Section 14.1). Different TCs are applicable because the vineyard properties are different, e.g., regarding the degree of pruning, influencing the amount of foliage available for dermal contact at the time of *harvesting, tying/training or leaf pulling*, or the degree or irrigation, influencing the amount of NMP residue remaining on leaves, e.g., at the time of harvesting. Therefore, in the same crop, different TCs for different activities logically results in different exposure doses (Table 14.4.2.3).

The main result to be noted from Table 14.4.2.3 is that all post-application re-entry activities are associated with NMP dose levels that are not associated with a risk to health or reproductive effects, since all MOEs are higher than the LOC. Therefore, it is concluded that a risk to the health of post-application re-entry workers is not expected, regardless of the type of activity or the type of crop.

15.1.3 Uncertainty and the level of confidence

The toxicity values, that is, the PODs used to determine whether the calculated exposure doses are likely or unlikely to be associated with a risk to health, are those used by the USEPA for NMP risk assessments. The PODs were selected by the USEPA, based on a comprehensive literature review of available scientific studies. Thus, the degree of confidence in the POD values is relatively high, and the PODs are all applicable to developmental toxicity effects, which are the hazard of concern for NMP in WARLOCK® 19.2 EC.

The health risk assessment is conducted using guidelines, methods and equations regularly used by the USEPA for pesticide risk assessments. These methods and equations are supported by documented and verifiable research reports or standard operating procedures ("SOPs") for this type of risk assessment.

Conservative exposure parameter values were used throughout the assessment and for all relevant calculations, e.g.:

- A conservative upper-end estimate of the total spray solution volume for backpack applications.
- Assumption of a high-volume application on fruit trees in full leaf (high leaf density).
- The upper limit unit volume is used for the risk assessment on grapes, assuming a vineyard with a full-leaf canopy.
- Tree-row-volume calculations for fruit trees were calculated assuming higher-end tree heights and limb spread, and lower-end row spacing, which would yield conservative, higher-end volumes, resulting in high required spray volumes per hectare.
- Throughout the assessment, calculations were done with the highest concentration of 0.3 kg NMP/litre product, while the lower end of the concentration range is only 0.1 kg/litre. Therefore, the "true" NMP concentration was likely overestimated (and never underestimated) in all of the calculations.

In combination, the choice of conservative exposure assumptions detailed above may result in an overestimation of the exposure dose, but is highly unlikely to result in an underestimation.

In summary, the results and conclusions in this report are presented with confidence.

16 Summary of conclusions

- Pesticide use of WARLOCK® 19.2 EC is claimed for:
  - Vines: table and wine grapes
  - Apples and pears
  - Citrus fruit
  - Pomegranates
  - Stone fruit
  - Groundnuts
  - Maize and sweetcorn
  - Sunflowers
  - Tomatoes.

- Operators mixing and loading WARLOCK® 19.2 EC solutions for application by groundboom broadcast spraying are exposed to levels of NMP that are not associated with a risk to health (including reproductive effects).

- Operators applying the prepared solutions by groundboom broadcast spraying are also not exposed to NMP levels associated with an effect on health.

- Backpack operators mixing, loading and spraying solutions with WARLOCK® 19.2 EC concentrations according to label instructions are exposed to levels of NMP that are not associated with a risk to health, including of reproductive effects.

- Post-application re-entries after 12 hours for the purpose of various activities while tending to crops are not associated with a risk to health (or reproductive effects).

- The above assessment is based on PPE use as specified on the WARLOCK® 19.2 EC label, namely protective gloves, protective clothing, eye protection and face protection. Protective clothing is assumed to mean an additional layer of protection, not only the usual clothing such as pants, a shirt, socks and closed shoes. The assumed additional layer is a water repellent woven coverall, and boots protecting against harmful chemicals (Section 14.2).

- Respiratory protection is also recommended on the WARLOCK® 19.2 EC label, but detailed specifications are not provided. It is assumed that respiratory protection would provide the default level of 90 per cent protection, resulting in penetration of only 10 per cent of the inhalable load.

- NMP has a low hazard profile for ecological receptors, and it exhibits low persistence and bioaccumulation if released into aquatic or terrestrial compartments. The USEPA has assessed NMP as of low acute and chronic toxicity to aquatic organisms and birds, based on study data evaluated as of high quality. No further evaluation of ecological risks is required. NMP is known to be highly toxic to larval honey bees; therefore, adherence to the use restriction on the WARLOCK® 19.2 EC label is vital: "*Do not use WARLOCK® 19.2 EC during flowering and when bees are actively foraging, as the product can be toxic to bees*."

17 Recommendations

An application for the restricted use of the NMP-containing commercial pesticide WARLOCK® 19.2 EC should be granted according to the intended product use:

- Pesticide not for sale to and used by residential gardeners.
- Preparation and application of the spray solution in accordance with the instructions on the product label.
- Personal hygiene instructions on the SDS must be followed; that is, "*wash face, hands and any exposed skin thoroughly after handling*", "*Do not eat, drink or smoke when using this product*", etc.
- Double-layered clothing must be worn when mixing/loading or applying the product; that is, a coverall over basic clothing and chemical-resistant gloves and shoes (e.g., rubber boots).
- Respiratory protection shall be used when mixing/loading or applying the product.
- Label re-entry instructions must be followed, namely, to enter only after applied product has dried off the treated crop and foliage.

- Adherence to the use restriction on the WARLOCK® 19.2 EC label is vital: "*Do not use WARLOCK® 19.2 EC during flowering and when bees are actively foraging, as the product can be toxic to bees*."

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19 Annexure 1

Table A1: Post-application agricultural workers residue transfer coefficients.

Crop group USEPA TC Table	Crop or Target	Crop description in USEPA TC Table	Activity	Transfer coefficient (TC)
				cm^2/hr
Vine / trellis	Vineyard	Grape, table	Girdling / Turning	19 300
Vine / trellis	Vineyard	Grape, juice / wine	Harvesting hand, Tying / training, Leaf pulling	10 100
Vine / trellis	Vineyard	Grape, raisin / table	Harvesting hand, Tying / training, Leaf pulling	5 500
Vine / trellis	Vineyard	Grape, table / raisin / juice / wine	Pruning / weeding by hand, Scouting, propagating	640
Vine / trellis	Vineyard	Grape, table / raisin / juice / wine	Irrigation hand set	1 900
Vine / trellis	Vineyard	Grape, table / raisin / juice / wine	Transplanting	230
Vine / trellis	Vineyard	Grape, table / raisin / juice / wine	Irrigation (non-hand set) & All mechanised activities	0
Tree, "fruit", deciduous	Pome fruit	Apples, Pears	Thinning fruit	3 600
Tree, "fruit", deciduous	Pome fruit	Apples, Pears	Harvesting by hand	1 400
Tree, "fruit", deciduous	Pome fruit	Apples, Pears	Pruning by hand	580
Tree, "fruit", deciduous	Pome fruit	Apples, Pears	Weeding by hand, Propping, Orchard maintenance	100
Tree, "fruit", deciduous	Pome fruit	Apples, Pears	Irrigation (non-hand set) & All mechanised activities	0
Tree, "fruit", deciduous	Stone fruit	Apricot, Cherries, Peaches, Nectarine	As for Pome fruit	As for Pome fruit
Tree, "fruit", deciduous	Pomegranate	Pomegranate, Crop height “high”, foliage density “full”	Harvesting by hand	1 400
Tree, "fruit", deciduous	Pomegranate	Pomegranate, as above	Scouting, pruning by hand	580
Tree, "fruit", deciduous	Pomegranate	Pomegranate, as above	Transplanting	230
Tree, "fruit", deciduous	Pomegranate	Pomegranate, as above	Weeding by hand, orchard maintenance	100
Tree, "fruit", deciduous	Pomegranate	Pomegranate, as above	Irrigation (non-hand set) & All mechanised activities	0

Crop group USEPA TC Table	Crop or Target	Crop description in USEPA TC Table	Activity	Transfer coefficient (TC)
				cm^2/hr
Tree, "fruit", evergreen	Citrus	Orange, Grapefruit, Lemon	Harvesting hand	1 400
Tree, "fruit", evergreen	Citrus	Orange, Grapefruit, Lemon	Pruning hand, Scouting	580
Tree, "fruit", evergreen	Citrus	Orange, Grapefruit, Lemon	Transplanting	230
Tree, "fruit", evergreen	Citrus	Orange, Grapefruit, Lemon	Weeding by hand / Orchard maintenance	100
Tree, "fruit", evergreen	Citrus	Orange, Grapefruit, Lemon	Irrigation (non-hand set) & All mechanised activities	0
Field/row crops, height “low”, foliage density “full”	Groundnuts	Peanut	Irrigation hand set	1 900
Field/row crops, as above	Groundnuts	Peanut	Scouting	210
Field/row crops, as above	Groundnuts	Peanut	Weeding hand	70
Field/row crops, as above	Groundnuts	Peanut	Harvesting, mechanical, irrigation (non-hand set) & all mechanised activities	0
Field / row crop, tall	Maize	Corn, field, grain. Crop height “high”, foliage density “full”	Irrigation, hand set	1 900
Field / row crop, tall	Maize	Corn, field, grain, as above	Scouting	1 100
Field / row crop, tall	Maize	Corn, field, grain, as above	Weeding by hand	70
Field / row crop, tall	Maize	Corn, field, grain, as above	Harvesting, mechanical, irrigation (non-hand set) & all mechanised activities	0
Field / row crop, tall	Sweetcorn	Corn, field/pop/sweet, seed. Crop height “high”, foliage density “full”	Detasseling (hand and mechanically-assisted)	8 800
Field / row crop, tall	Sweetcorn	Corn, field/pop/sweet, seed, as above	Irrigation, hand set	1 900
Field / row crop, tall	Sweetcorn	Corn, field/pop/sweet, seed, as above	Scouting	1 100
Field / row crop, tall	Sweetcorn	Corn, field/pop/sweet, seed, as above	Weeding by hand	70
Field / row crop, tall	Sweetcorn	Corn, field/pop/sweet, seed, as above	Harvesting, mechanical, irrigation (non-hand set) & all mechanised activities	0

Crop group USEPA TC Table	Crop or Target	Crop description in USEPA TC Table	Activity	Transfer coefficient (TC)
				cm^2/hr
Field / row crop, tall	Sunflower	Sunflower	Scouting and bird control	90
Field / row crop, tall	Sunflower	Sunflower	Harvesting, mechanical	0
Vegetable, fruiting	Tomato	Tomato	Irrigation, hand set	1 900
Vegetable, fruiting	Tomato	Tomato	Harvesting by hand, Tying/Training,	1 100
Vegetable, fruiting	Tomato	Tomato	Transplanting	230
Vegetable, fruiting	Tomato	Tomato	Scouting	210
Vegetable, fruiting	Tomato	Tomato	Weeding by hand	70
Vegetable, fruiting	Tomato	Tomato	irrigation (non-hand set) & all mechanised activities	0