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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 SPHINX® EXTRA WG

Report No 044-2024 Rev 1.0

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31 October 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.

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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 October 2024

Internal review
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List of Abbreviations

AEL	Acceptable exposure level
AR	Applied radioactivity
BCF	Bioconcentration factors
CDC	Centers for Disease Control and Prevention
CMR	Carcinogenicity, mutagenicity, and reproductive toxicity
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemical's
EDSP	Endocrine Disruptor Screening Program
EEC	Estimated environmental concentration
EFSA	European Food Safety Authority
EIIS	Ecological Incident Information System
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA SF	Food Quality Protection Act Safety Factor
FRAC	Fungicide Resistance Action Committee
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HED	Human equivalent dose
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
NOAELs	No-observed-adverse-effect levels
NRC	US National Research Council
OC	Organic carbon
OECD	Organisation for Economic Co-operation and Development
OPP	USEPA Office of Pesticide Programs
PAD	Population adjusted dose (a = acute, c = chronic)
POD	Point of departure
REACH	Registration, evaluation and authorization of chemicals
RfD	Reference dose
RQ	Risk quotient
SENSOR	Health Sentinel Event Notification System for Occupational Risk-Pesticides
SI	Standard International
STOT RE	Specific target organ toxicity (repeated exposure)
TRA	Targeted Risk Assessment
TSCA	Toxic Substances Control Act
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
WDG	Water-dispersible granule

List of Terms

Aerobic metabolism	Metabolism, including the production of cellular energy, with the consumption of oxygen
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.
Foliar	On or of the leaves of a plant
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 it poses by these chemicals
Mutagenicity	Property of chemical agents to induce genetic mutation
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.
Receptors	People exposed to the substance of interest
Registrar	Registrar of the Department of Agriculture, Land Reform and Rural Development, responsible for applying Act 36 of 1947
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.
Synthetase	Enzyme catalysing the joining of two molecules, with concomitant energy expenditure
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 fungicide SPHINX® EXTRA WG, with Act 36 of 1947 registration number L9294.

SPHINX® EXTRA WG is identified as a substance of concern due to its classification as a reproductive hazard category 1B (H360F) according to the Globally Harmonized System of Classification and Labelling of Chemicals ("GHS"). The classification is due to the ingredient dimethomorph, which is classified in GHS as a reproductive toxicity hazard category 1B (H360F).

Prepared for: ADAMA South Africa (Pty) Ltd
Product name: SPHINX® EXTRA WG
Act 36 of 1947 registration number: L9294

Intended product use:

- A preventive contact translaminar water dispersible granule fungicide for the control of downy mildew on table and wine grapes.
- The product is for use in large-scale agricultural crop production enterprises.
- 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.

Occupational exposure risk assessment:
Two occupational designations are assessed, exposed by the dermal and inhalation routes of exposure:

- Occupational pesticide handlers, responsible for mixing, loading and application of the fungicide.
- Post-application (re-entry) workers, exposed by the dermal and inhalation routes.

The product supplier has indicated that the fungicide is not intended for aerial application (e.g., by low-flying aircraft) and this method of application is excluded from the assessment. The most practical method of application is groundboom spraying, which is assessed in this report. Completely mechanised post-application re-entry activities are highly unlikely to be associated with any significant exposure to workers and are not assessed.

Occupational health risk assessment results
The results of the health risk assessment indicated that there are not reasons for concern, including of reproductive/developmental toxicity effects, in agricultural operators handling the product, mixing or applying the product, or workers in contact with treated crops after the spray has dried off, according to instructions on the SPHINX® EXTRA WG label.

Non-occupational bystanders
These are individuals nearby agricultural pesticide applications. Assuming basic agricultural management practices in the event of pesticide application, it is highly unlikely that bystanders will be directly exposed to spray or spray drift by skin contact or inhalation. Volatilisation of pesticides may be a source of post-application inhalation exposure to non-occupational bystanders. Risks to health, including reproductive/developmental toxicity effects, are not indicated in this scenario.

Exposure to spray drift
Health risks associated with spray drift exposure is assessed for children, the most sensitive

receptors. The assessed scenario is spray drift deposition on nearby grass, where a young child is assumed to play in the grass. Dermal exposure to deposited residues does not pose a risk to health, because dimethomorph is not hazardous by the dermal route of exposure. Incidental oral risks were assessed for hand-to-mouth ingestion of dimethomorph spray drift residues deposited on grass, and the dose ingested in this way is too low to present a risk to health, including of reproductive/developmental effects.

Dietary exposure to treated crops

The risk of a health effect in consumers eating treated crops, and/or drinking water potentially impacted by agricultural applications of SPHINX® EXTRA WG, was examined. A risk to health, including of reproductive/ developmental effects, is not indicated.

Ecological risks

Mammals foraging in treated crops are not at risk due to short-term exposure, and the potential of adverse effects from chronic exposure is low. The likelihood of adverse effects from acute or chronic exposure to birds, terrestrial-phase amphibians and reptiles is anticipated to be low. Dimethomorph is practically nontoxic to young adult honey bees, but data on larval bees or chronic toxicity to adult bees are not available. Non-target plants are unlikely to be damaged by contact with dimethomorph. Freshwater fish, aquatic-phase amphibians and aquatic invertebrates are not expected to be adversely affected in the agricultural use scenario. These ecological assessments are relevant to the correct use of SPHINX® EXTRA WG, according to label instructions, including label directions to protect the environment.

Restricted use application

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

- Fungicide not for sale to and use by residential gardeners.
- Preparation and application of the treatment solution in accordance with instructions on the product label.
- Personal hygiene instructions on the product label must be followed, that is, washing hands, forearms and face thoroughly after handling chemical products.
- Wearing protective gloves, protective clothing, eye protection and face protection, as directed on the SPHINX® EXTRA WG label, is sufficiently protective if handling and application of the fungicide is according to label instructions.
- Treated crop must not be entered before spray has dried off, according to label instructions.

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 SPHINX® EXTRA WG.

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

Section 3 lists the composition of SPHINX® EXTRA WG, summarised from the product label.

Section 4 describes hazard identification of the constituents of SPHINX® EXTRA WG, showing that dimethomorph is the active ingredient that is relevant in the CMR assessment.

Section 5 outlines the essential, concise steps of the health risk assessment paradigm.

Section 6 explains the fungicide action and benefits assessment of dimethomorph.

Section 7 explains more details of the human health risk assessment methodology followed in this assessment report.

Section 8 provides an environmental fate assessment for dimethomorph.

Section 9 summarises toxicological reviews and presents toxicological parameters for application in health risk assessment.

Section 10 provides information on endocrine screening assessments.

Section 11 summarises recorded human incident reports.

Section 12 presents an overview of ecological risk assessment

Section 13 deals with recorded ecological incidents.

Section 14 describes occupational exposure calculations and results.

Section 15 describes dietary exposure and risk assessment.

Section 16 presents a summary of conclusions.

Section 17 presents recommendations for granting of derogation.

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

3 Composition of SPHINX® EXTRA WG

Active ingredients:
Dimethomorph (cinnamic acid amides) 113 g/kg
Folpet (phthalimides) 600 g/kg

The formulation has the composition listed in Table 3.1.

Table 3.1: Composition of SPHINX® EXTRA WG.

Chemical name	Per cent (w/w)	CAS #
Folpet	10 - 30	133-07-3
Dimethomorph	> 60	110488-70-5
Benzenesulfonic acid, hydroxy-, polymer with formaldehyde, phenol and urea, sodium salt	< 10	102980-04-1
Alkylnaphthalenesulfonic acid, polymer with formaldehyde, sodium salt	< 10	68425-94-5
Disodium maleate	< 10	371-47-1

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 active ingredients and their formulations that meet the criteria of CMR categories 1A or 1B in the GHS. Information in the GHS represents hazard data, not information on risk. All ingredients of SPHINX® EXTRA WG listed in Table 3.1 were submitted to hazard classification to assess the possible presence of CMR constituents.

4.2 Hazard classification of active ingredients

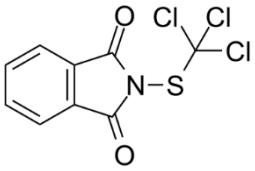	**Folpet** **CAS # 133-07-3**

Table 4.2.1: GHS classification of folpet.

Hazard class and category code	Hazard Statement Code	Hazard statement	Signal word	Pictogram
Eye Irrit. 1	H319	Causes serious eye irritation	Warning	
Skin Sens. 1	H317	May cause allergic skin reaction	Warning	
Acute Tox. 4	H332	Harmful if inhaled	Warning	
Carc. 2	H351	Suspected of causing cancer	Warning	
Aquatic Acute 1	H400	Very toxic to aquatic life	Warning	

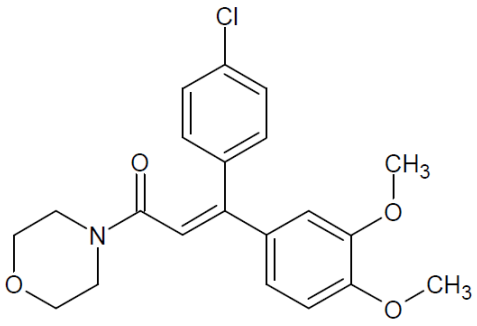	**Dimethomorph** **CAS # 110488-70-5**

Table 4.2.2: GHS classification of dimethomorph.

Hazard class and category code	Hazard Statement Code	Hazard statement	Signal word	Pictogram
Repr. 1B	H360F	May damage fertility	Danger	
Aquatic Chronic 2	H411	Toxic to aquatic life with long lasting effects	No signal word	

GHS Category 1B criteria for substance classification are:

- 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 is not considered to be a second non-specific consequence of the other toxic effects.

4.3 Hazard assessment for other ingredients

Hazard classifications of the non-active ingredients are listed in Table 4.3.1.

Table 4.3.1: GHS classification of non-active ingredients.

Hazard class and category code	Hazard Statement Code	Hazard statement	Signal word	Pictogram
Benzenesulfonic acid, hydroxy-, polymer with formaldehyde, phenol and urea, sodium salt				
Aquatic Chronic 3	H412	Harmful to aquatic life with long lasting effects.	None	None
Alkylnaphthalenesulfonic acid, polymer with formaldehyde, sodium salt				
Skin Irrit. 2	H315	Causes skin irritation	Warning	
Eye Irrit 2	H319	Causes serious eye irritation		
Disodium maleate				
Acute Tox. 4	H302	Harmful if swallowed	Warning	
Skin Irrit. 2	H315	Causes skin irritation		
Skin Sens. 1	H317	May cause an allergic skin reaction		
Eye Irrit. 2	H319	Causes serious eye irritation		
STOT SE 3	H335	May cause respiratory irritation		

4.4 Project focus

The need for derogation is applicable to CMR categories 1A or 1B. Folpet is classified as carcinogenic category 2; therefore, derogation is not required for folpet (Table 4.2.1). Also, no CMR hazards have been identified for the non-active ingredients of SPHINX® EXTRA WG (Table 4.3.1).

The health risk assessment for derogation thus considers only dimethomorph, classified as a reproductive toxicant, as indicated in Table 4.2.2. It is a mixture of two isomers (E and Z), but only the Z isomer has fungicidal activity.

5 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 assessment, 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) refers 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 4.1 illustrates the health risk assessment paradigm in a simple diagram.

[1] Registration, evaluation and authorization of chemicals.
[2] http://www.ecetoc.org/tools/targeted-risk-assessment-tra/.

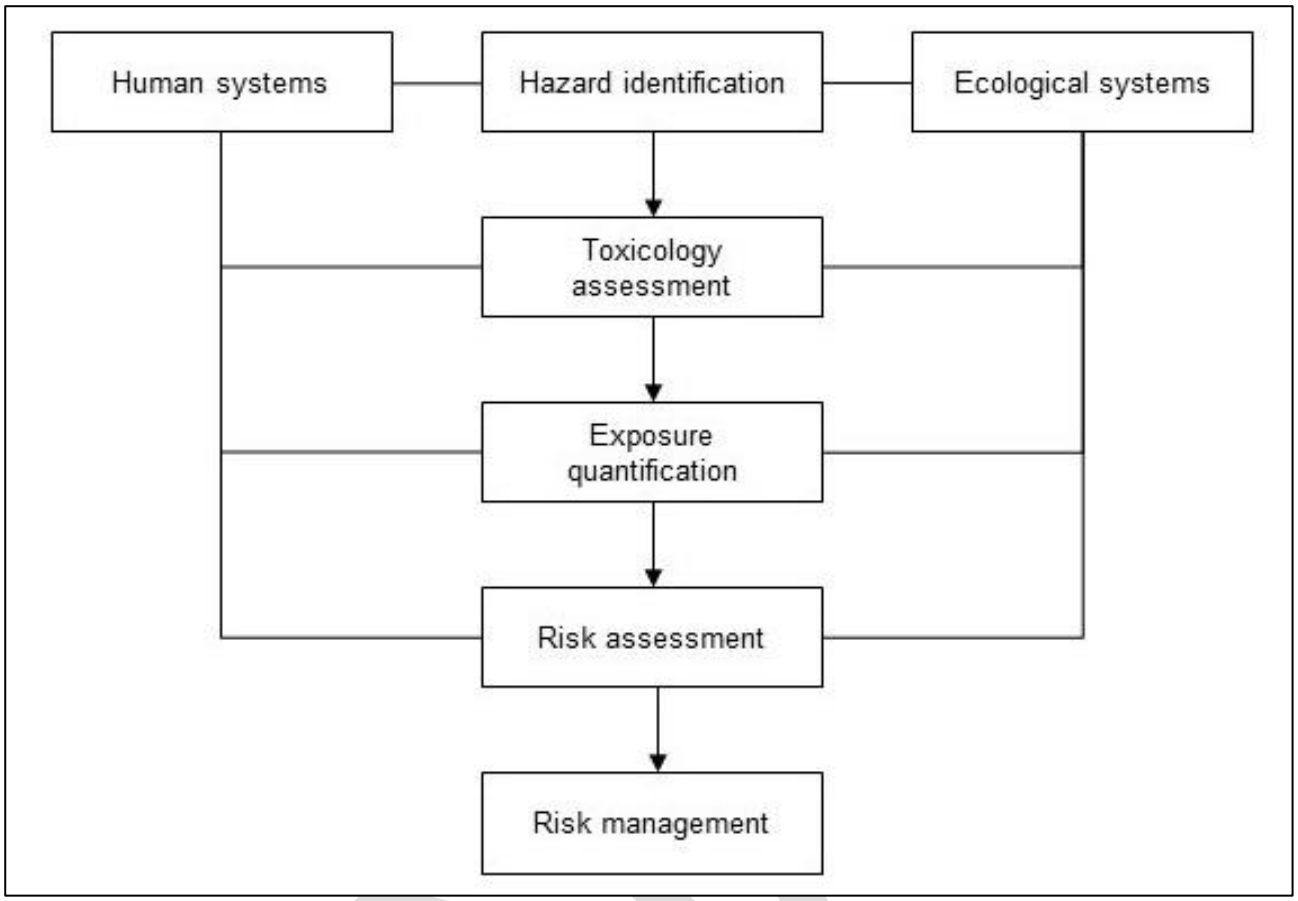

Figure 4.1: The holistic health risk assessment paradigm.

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.

6 Fungicide action and benefits assessment

SPHINX® EXTRA WG is formulated as a water-dispersible granule ("WG"). It is a broad-spectrum, non-systemic protectant pesticide used as a fungicide to control fungal foliar diseases on a variety of agricultural crops, in addition to ornamental plants, trees, conifers, and turf in sod farms, golf course and commercial/non-residential areas. Residential uses include golf courses and use on home gardens. The mode of action is on cell wall synthesis, with cellulose synthase as the target.

Dimethomorph is a fungicide option in FRAC[3] Group 40, which has a low-to-medium risk of resistance development (FRAC Code List© 2024). Certain fungicidal alternatives to dimethomorph have a propensity for developing resistance. Dimethomorph is a key product in rotational programmes for managing resistance, and in cases where multiple fungicide treatments are necessary. Dimethomorph can be used up to the end of the growth season, which is an advantage over other fungicides with longer preharvest intervals. It is a key product for the control of late blight in potatoes, downy mildew in iceberg lettuce, and other *Phytophthora* diseases. *Phytophthora* species make up a group of microorganisms that are plant pathogens. Certain species of *Phytophthora* cause major diseases in vegetable crops, fruit and nut trees, and forest trees, as well as in nursery crops. Dimethomorph is a key product in controlling these diseases, with limited risk of resistance development.

[3] Fungicide Resistance Action Committee

7 Human health risk assessment methodology

The HHRA paradigm divides human health risk assessment into a number of logical steps. 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 dimethomorph and the reproductive/developmental toxicity hazard.

- **Dose-response assessment** (toxicological assessment) addresses the relationship between levels of uptake and the manifestation of adverse effects (reproductive/developmental toxicity). For this purpose, the following INFOTOX actions are needed:

    - Collection of human reproductive toxicity data on dimethomorph from scientific publications.

    - Retrieval of toxicological information from available reproductive/ developmental studies, and will apply standard risk assessment methodologies to derive a point of departure ("POD") and level of concern ("LOC") or acceptable exposure level ("AEL") 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 effects of the product. This will ensure 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 will be 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 will be constructed to guide the exposure assessment for the health risk assessment.

    The HHRA considers the following <u>occupational exposure</u> scenarios:
    - The dermal and inhalation routes of exposure of fungicide mixers and applicators.
    - The dermal and inhalation post-application exposure of workers re-entering treated fields.

    <u>Residential handler exposure</u> scenarios are not assessed, because the fungicides assessed with the methodology explained in this report is not for sale in retail outlets catering to the general public.

Spray drift exposure of non-occupational receptors in the occupational setting is assessed, which may result in exposures to adults and children to dimethomorph. Incidental contact with spray drift residues deposited on neighbouring residential lawns is also assessed, particularly for children.

Dietary exposure, by the ingestion of fungicide residues in fruit and vegetable crops, is considered for consumers, including children.

INFOTOX covers the occupational and dietary exposure scenarios in the health risk assessment, referring to published risk assessment studies.

- **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.

8 Environmental fate assessment

8.1 Summary of physical and chemical properties of dimethomorph

Physical/chemical properties and aspects of environmental fate are summarised in Table 8.1.1. Numerical values were adopted from USEPA (2016a) but, for consistency, the values were converted to Standard International ("SI") units, which are the units that INFOTOX applies in environmental fate calculations, adopted from Mackay et al. (1992).

Table 8.1.1 lists USEPA MRID references. The USEPA uses Master Record Identifiers ("MRIDs") to track and manage information submitted to the Pesticide Programs[4]. Table 8.1.1 lists USEPA MRID references. An MRID is unique eight-digit number assigned to each study submitted to USEPA. The first six digits are referred to as the 'root' MRID. Some of the studies have not been published in the open scientific literature, but USEPA evaluate the integrity of all studies, and information is used only from studies that are classified as acceptable. USEPA also refers to accession numbers ("Acc No") to access data from the non-confidential Toxic Substances Control Act ("TSCA") Inventory.

The USEPA often references MRID numbers in assessment reports of the Pesticide Programs, but do not always provide the complete study reference. Therefore, Table 8.1.1 does not refer to specific MRID numbers.

[4] https://www.epa.gov/pesticide-registration/study-formatting-and-supplemental-information#establish%20MRID.

Table 8.1.1: Physical/chemical properties of dimethomorph that determine its environmental fate (USEPA 2016a).

Property	Value	Comments
Physical/chemical parameters		
Molecular weight (g/mol)	387.86	
Solubility in water (mg/litre, 20°C)	28.95	Low water solubility
Vapour pressure (mPa)	E isomer 9.7E-07 Z isomer 10.0E-07	Non-volatile
Henry's law constant (Pa m^3 mol^{-1})	5.0E-04	Non-volatile
Octanol-water partition coefficient (Log K_{OW})	2.68	Low hydrophobicity
Persistence		
Hydrolysis half-life, 25 ºC at pH 4, 7 and 9	Stable	Stable at all pHs for a period of 10 weeks.
Aqueous photolysis half-life (pH 5, 25°C) (days)	50-56	Corresponds to 12-hour photo cycle in midsummer, uncorrected half-life with continuous irradiation was 25-28 days.
Soil photolysis half-life (25°C) (days)	75	Continuous irradiation (15 days) with a Xenon arc lamp
Aerobic soil metabolism half-life (20°C) (days)	66 117	Studies under the USEPA Pesticides Programss (MRID)
Anaerobic aquatic metabolism half-life (20°C) (days)	0.9, 1.3 18.2, 18.2	Studies under the USEPA Pesticides Programs (MRID)
Aerobic aquatic metabolism half-life (20°C) (days)	24.7 56.9	Studies under the USEPA Pesticides Programs (MRID)
Mobility		
Freundlich soil-water partition coefficients (K_d) (litre/kg)	4.47, 11.67, 2.09, 4.94, 8.51, 2.72, 3.03, 15.7, 10.1, 19.0, 11.9	Various foreign soils. The last four are for US soils.
Organic carbon-normalised Freundlich coefficients (K_{FOC}) (litre/kg_{OC})	566, 402, 290, 515, 377, 388, 316, 1 588, 1 158, 1 485, 787	Studies under the USEPA Pesticides Programs (MRID) Moderate-slightly mobile
Field dissipation		
Terrestrial field dissipation half-life (residues leaching depth)	44.4 days (not detected below 7.5-15 cm) 21.2 days (not detected below 15-30 cm) 9.8 days (not detected below 15-30 cm) 122 days (not detected below 30-45 cm)	Studies under the USEPA Pesticides Programs (MRID)
Fish bioconcentration		
Fish bioconcentration factors (BCF); depuration rate	No data	Data requirement was waived because the K_{ow} is <1 000

8.2 Overview

8.2.1 Physical/chemical parameters

Dimethomorph has low water solubility and is not volatile, which limits accumulation of high concentrations in water and air compartments.

Due to its low hydrophobic tendency, the data requirement for bioconcentration in fish was waived. K_{ow}, is below 1 000 (log K_{OW} below 3), and dimethomorph is not expected to bioconcentrate in fish.

8.2.2 Persistence

Dimethomorph did not hydrolyse in a period of 10 days over the pH range 4 to 9 in a study submitted in the US pesticide registration programme. It is considered likely that microbial metabolism is the primary route of dissipation (EFSA 2006), with reported laboratory aerobic soil metabolic half-lives of 66-to-117 days (USEPA 2016a). No aerobic soil metabolism degradation products were identified other than small amounts of radioactive tracer CO_2. As dimethomorph degrades rapidly, most of the radioactivity was not extracted from the soil.

Dimethomorph degraded in anaerobic soil and anaerobic aquatic systems, but the rates could not be determined because the studies had additional carbon sources that may have significantly accelerated the degradation rates. Two isomers (mono-desmethyl compounds) formed as intermediates from demethylation of dimethoxyphenyl in anaerobic studies, with combined amounts ranging from 2.1 to 9.1 per cent applied radioactivity (AR). The major degradation product of dimethomorph reported in environmental fate studies was carbon dioxide (CO_2) (aerobic soil metabolism, and anaerobic and aerobic aquatic metabolism) (USEPA 2016a, EFSA 2006).

8.2.3 Mobility

Dimethomorph was shown to be moderately mobile to slightly mobile in soil. The normalised organic-carbon-to-water partition coefficient (K_{OC}) is described as the ratio between the distribution coefficient K_d, and the organic carbon content of the sorbent, in units of mass of organic carbon ("OC") per mass of soil (g OC/g soil).

$$K_{FOC} = {}^{K_d}/_{OC} \qquad \text{Equation 8.2.3.1}$$

Where:

K_{FOC}	Normalised organic-carbon-to-water partition coefficient
K_d	Soil-water distribution coefficient
OC	Mass of organic carbon per mass of soil

Mobility in German soils were reported (K_d values were 2.09 to 11.67 litre/kg and K_{oc} values were 290 to 566) (Table 8.1.1). Mobility in the four selected USA soils had K_d values range of 10.1-19.0 ml/g, and K_{oc} values range of 787 to 1 588 (Table 8.1.1).

8.2.4 Dissipation

Four field dissipation studies showed that dimethomorph degraded in the field with half-lives that range from 1.4-to-122 days, with no leaching detected below 30 cm (Table 8.1.1).

9 Toxicological reviews

9.1 Background to toxicological information systems

See Section 8.1 for an explanation of references to studies carried out under the US Pesticide Programs.

9.2 Toxicological summary for dimethomorph

Health Effects Division ("HED") in the USEPA Office of Pesticide Programs evaluated the scope of work necessary to assess the fungicide dimethomorph for Registration Review, and determined that the risk assessment for dimethomorph, conducted in July of 2015 (USEPA 2015, Memorandum from Sumitra Bose Biswas, 28 July 2015), provided an up-to-date assessment of dimethomorph, relating to its toxicity, dietary, and aggregate risk status (USEPA 2016b, memo from Sheila Piper et al., 2 August 2016).

For the Registration Review, HED considered it necessary to provide an update on the occupational exposure assessment, as well as a spray drift assessment for dimethomorph. The occupational risk assessment and spray drift assessment were provided under separate memo (USEPA 2016c, Memorandum from Monica Hawkins). The July 2015 risk assessment and the updated occupational and spray drift assessments (USEPA 2016c) constitute the draft risk assessment for the purpose of registration review.

USEPA (2018) provides summaries of human and ecological risks in the Registration Review Decision.

9.3 Acute dietary endpoint - general population

Dimethomorph has low acute toxicity by the oral, dermal, and inhalation routes of exposure. It is not an eye or skin irritant, and is not a skin sensitiser (USEPA 2015).

An acute neurotoxicity study in rats was selected for risk assessment, based on reduced motor activity and impairment of gait and rearing in both sexes observed at the lowest daily dose tested (LOAEL = 250 mg/kg-day). The route and a single exposure of this study were assessed as appropriate for acute dietary risk assessment. A total safety factor of 1 000 was applied (10x for extrapolation from animal data to humans, and 10x to account for variation in susceptibility among members of the human population). A Food Quality Protection Act ("FQPA") Safety Factor ("SF") of 10x was applied, because of uncertainty in extrapolating from a LOAEL to a NOAEL.

An acute reference dose ("aRfD") was thus derived as 0.25 mg/kg-day. The acute population-adjusted dose ("aPAD") is also 0.25 mg/kg-day. The PAD is the maximum acceptable dose that is not expected to result in unreasonable adverse health effects, including of reproductive effects, as determined by the USEPA.

9.4 Acute dietary endpoint - females 13-to-49 years of age

No appropriate endpoint was identified for acute dietary risk assessment in this population group.

9.5 Chronic dietary endpoint (all populations)

Rat chronic and carcinogenicity studies had similar NOAELs (11.9 versus 11.3 mg/kg-day) and endpoints with increased incidences of pigmented or hypertrophied hepatocytes, and "ground glass" foci in livers of female rats at LOAELS of 99.9 and 46.3 mg/kg-day, respectively. The studies were considered co-critical in establishing a POD of 11 mg/kg-day for chronic dietary risk assessment. An SF of I00x was applied (10x for interspecies extrapolation, 10x for intraspecies variation, and 1x for the FQPA SF). A chronic reference dose ("cRfD") of 0.11 mg/kg-day was obtained. The cPAD is also 0.11 mg/kg-day.

9.6 Incidental oral short-term (1 to 30 days)

A subchronic toxicity study in dogs was selected for short-term incidental oral exposure. The NOAEL was 15 mg/kg-day, and the LOAEL was 43 mg/kg-day, based on decreased absolute and relative prostate weights. An uncertainty factor of 100x was applied (10x for interspecies extrapolation, 10x for intraspecies variation, and 1x for the FQPA SF). An LOC (MOE) was recommended by the USEPA (2015).

9.7 Dermal short-term (1 to 30 days), and intermediate term (1 to 6 months)

A quantitative dermal risk assessment for short- and intermediated-term occupational, dermal exposure was not considered necessary by USEPA (2015) since no toxicity was observed at the limit dose (I 000 mg/kg-day) in a 28-day dermal toxicity study in the rat, and no developmental toxicity concern has been identified (see also Table 9.11.1).

9.8 Dermal long-term (> 6 months)

Normal use of dimethomorph cannot lead to long-term dermal exposure.

9.9 Acute, short- and intermediate-term inhalation endpoint

Other than an acute inhalation study, no data from a subchronic inhalation study was available. Accordingly, USEPA (2015) selected the subchronic oral toxicity study in dogs for short and intermediate-term inhalation exposure. There are no uses for dimethomorph that result in long-term inhalation exposure; therefore, a long-term inhalation risk assessment is not required.

The NOAEL in the selected study was 15 mg/kg-day and the LOAEL was 43 mg/kg-day, based on decreased absolute and relative prostate weights. Since an oral study was selected, the inhalation exposure component (µg ai/day) using 100 per cent absorption rate was converted to an equivalent oral dose (mg/kg-day) for risk assessment. An uncertainty factor of 1 000x was applied (10x for interspecies extrapolation, and 10x to provide a more accurate evaluation of inhalation risk. In the absence of the inhalation study a database uncertainty factor of 10x was applied.

An LOC (MOE) of 1 000 was recommended by USEPA (2015).

9.10 Inhalation long-term (> 6 months)

There is no long-term exposure to dimethomorph during normal use.

9.11 Cancer (oral, dermal, inhalation)

Dimethomorph is classified as "*not likely to be carcinogenic to humans*" based on a lack of evidence of carcinogenicity in rats and mice, and there is no evidence of mutagenicity (USEPA 2015).

9.12 Updated occupational health risk assessment

9.12.1 Scope

This section provides an update on the occupational exposure assessment, as well as a spray drift assessment for dimethomorph. (USEPA 2016c, Memorandum from Monica Hawkins). The toxicological doses and health endpoints for occupational health risk assessment are presented in Table 9.12.2.1.

Occupational pesticide handlers (mixers, loaders and applicators) were assessed. Dermal contact was not assessed, since there is no hazard via the dermal route of exposure (see Sections 9.7 and 9.8), but the USEPA (2015 and 2016c) did perform an inhalation exposure and risk assessment for handlers.

The occupational exposure of post-application (re-entry) agricultural workers was not calculated, for the following reasons:

- Dislodgeable foliar residues, to which post-application workers may be exposed via the dermal route, do not present a hazard, since there is no hazard via the dermal route of exposure (see Sections 9.7 and 9.8). Therefore, the USEPA (2015 and 2016c) also did not conduct a dermal post-application risk assessment for dimethomorph.
- Inhalation exposure of post-application workers was considered. Potential inhalation exposure sources include volatilisation of sprayed dimethomorph and resuspension of dusts and/or particulates that contain the fungicide.
- It was reasoned (USEPA 2015) that inhalation exposure of mixers/handlers and applicators is likely to result in higher exposure than post-application exposure. It was expected that these handler inhalation exposure estimates would be protective of occupational post-application inhalation exposure scenarios, and the position of the USEPA has not since changed. Therefore, calculations of post-application re-entry inhalation exposure are not performed.

9.12.2 Toxicological review

The toxicological study used for assessment of incidental oral short-term exposure (1 to 30 days) is described in Section 9.6. As described in Section 9.9, the oral exposure study was the basis for the assessment of inhalation exposure, since data from a subchronic inhalation study was not available.

The NOAEL in the oral exposure study was 15 mg/kg-day and the LOAEL was 43 mg/kg-day based on decreased absolute and relative prostate weights. Since an oral study was selected, the inhalation exposure component (µg ai/day) using 100 per cent absorption rate was converted to an equivalent oral dose (mg/kg-day) for risk assessments. An uncertainty factor of 1 000x was applied (10x for interspecies extrapolation, 10x for intraspecies variation, 10x for database uncertainty).

Table 9.12.2.1: Summary of dimethomorph toxicological doses and endpoints for use in occupational health risk assessment.

Point of Departure (POD)	Uncertainty/FQPA Safety Factors	LOC for Risk Assessment	Study and Toxicological Effects
Incidental oral short-term (1-30 days)			
NOAEL = 15 mg/kg-day	UFA = 10x UFH = 10x FQPA SF = 1x	Residential LOC = 100	A subchronic toxicity study in dogs was selected for short-term incidental oral exposure. The NOAEL was 15 mg/kg-day, the LOAEL was 43 mg/kg-day based on decreased absolute and relative prostate weights.
Dermal (short- and intermediate-term)			
No toxicity was observed at the limit dose in a 28-day dermal toxicity study. No quantitative risk assessment is necessary since no dermal or developmental toxicity concern.			
Inhalation (short- and intermediate-term)			
NOAEL= 15 mg/kg-day (inhalation absorption factor = 100 %)	UFA = 10x UFH = 10x UFDB=10x	LOC = 1 000	Subchronic feeding study in dogs LOAEL = 43 mg/kg-day based on decreased absolute and relative prostate weights.
Cancer (oral, dermal, inhalation)	Dimethomorph is classified as “not likely” to be a human carcinogen		
Notes to table: Point of Departure (POD) = data point or estimated point, derived from observed dose-response data, and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed-adverse-effect level. LOAEL = lowest-observed-adverse-effect level. FQPA SF = FQPA Safety Factor. UF = uncertainty factor: UF_A = extrapolation from animal to human (interspecies); UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB}= Database uncertainty. LOC = level of concern.			

9.13 Non-occupational bystander post-application inhalation exposure and risk estimates

Direct exposure of non-occupational bystanders is not likely, based on the “*premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them*”. “Direct” would include inhalation of the spray plume or being sprayed directly. The premise was accepted by the USEPA (2016c) for the purposes of spray drift risk assessment, but is equally applicable to bystander exposures.

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. However, this should not exceed the inhalation exposure of handlers and post-application workers. Risks to non-occupational bystanders in a scenario of large-scale agricultural applications were thus indirectly assessed by comparison with the risks calculated for handlers.

9.14 Spray drift risk assessment

SPHINX® EXTRA WG is no currently registered for residential uses and a residential spray drift risk assessment is not conducted. However, a non-occupational exposure spray drift assessment was conducted by the USEPA (2016c).

The USEPA (2016c) approach to the spray drift risk assessment is based on a "*premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them*". "Direct" would include inhalation of the spray plume or being sprayed directly.

Rather, the USEPA (2016c) calculated indirect exposures of residential receptors through contact with areas impacted by spray drift, such as residential lawns, when compliant applications are conducted. Essentially, the USEPA conducted a residential lawn assessment based on exposure to spray drift deposited residues, from agricultural applications of dimethomorph**.**

There are no short- or intermediate-term dermal PODs, since dermal contact is not hazardous to health. Therefore, only incidental (hand-to-mouth) oral risk estimates were evaluated for children (1 to < 2 years old), that is, ingestion of agricultural spray drift residues deposited on residential lawns. The USEPA (2016c) risk estimates indicated no risks of concern at the field edge for groundboom applications, based on a dimethomorph application rate of 0.2 lb/A (0.224 kg/ha).

9.15 Summary of toxicological values for HHRA

A summary of values used for the dimethomorph HHRA is presented in Table 9.14.1.

Table 9.14.1: Summary of dimethomorph toxicological doses and endpoints for use in HHRA.

Point of Departure (POD)	Uncertainty/FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Incidental oral short-term (1-30 days)			
NOAEL = 15 mg/kg-day	UFA = 10x UFH = 10x FQPA SF = 1x	Residential LOC = 100	A subchronic toxicity study in dogs was selected for short-term incidental oral exposure. The NOAEL was 15 mg/kg-day, the LOAEL was 43 mg/kg-day based on decreased absolute and relative prostate weights.
Acute dietary (general population)			
LOAEL = 250 mg/kg-day	UF_A = 10x UF_H = 10x FQPA SF = 10x	aRfD = 0.25 mg/kg-day aPAD = 0.25 mg/kg-day	Acute neurotoxicity study in rats LOAEL = 250 mg/kg-day based on reduced motor activity and impairment of gait and rearing in both sexes
Acute dietary (general population including females 13-49 years of age)			
No appropriate endpoint was identified including developmental toxicity studies in rats and rabbits.			
Chronic dietary (all populations)			
PoD = 11 mg/kg-day	UF_A = 10x UF_H = 10x FQPA SF = 1x	cRfD = 0.11 mg/kg-day cPAD = 0.11 mg/kg-day	Co-critical chronic and carcinogenicity studies in rats LOAEL = 46.3 mg/kg-day, based on decreased body weight and increased liver lesions in female rats
Dermal short-term (1-30 days), and intermediate-term (1-6 months)			
No toxicity was observed at the limit dose in a 28-day dermal toxicity study. No quantitative risk assessment is necessary since no dermal or developmental toxicity concern.			
Dermal long-term (> 6 months)			
No long-term exposure.			
Inhalation acute, short-term (1-30 days), intermediate (1-6 months)			

Point of Departure (POD)	Uncertainty/FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Oral NOAEL = 15 mg/kg-day (Inhalation absorption factor = 100 %	UF_A = 10x UF_H = 10x FQPA SF = 10x	LOC 1 000	Subchronic feeding study in dogs LOAEL = 43 mg/kg-day, based on decreased absolute and relative prostate weights
Inhalation long-term (> 6 months)			
No long-term exposure			
Cancer (oral, dermal, inhalation)			
Dimethomorph is classified as "not likely" to be a human carcinogen.			
Notes to table: Source: USEPA (2015) Point of Departure (POD) = data point or estimated point. derived from observed dose-response data, and used to mark the beginning of extrapolation to determine risk 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). FQPA SF = FQPA Safety Factor. RfD= reference dose. cPAD = chronic population-adjusted dose. LOC = level of concern.			

10 Endocrine disruption

As required by the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") and the Federal Food, Drug, and Cosmetic Act ("FFDCA"), USEPA reviews studies of chemicals to assess potential adverse outcomes from exposure. Studies include acute, subchronic, and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. The studies cover endpoints that may be susceptible to endocrine effects, including endocrine target organ effects, histopathology, organ weights, oestrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring (USEPA 2021a). For ecological hazard assessments, USEPA evaluates acute and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups.

As required by the FFDCA, pesticide chemicals are subject to the endocrine screening part of the Endocrine Disruptor Screening Program ("EDSP") of the USA. The EDSP applies a two-tiered approach in assessing potential endocrine disrupting effects. Tier 1 consists of a set of 11 screening assays to identify the potential of a chemical substance to interact with the oestrogen, androgen, or thyroid ("E, A, or T") hormonal systems. Chemicals that show the potential to interact with E, A, or T hormonal systems in Tier 1 screening proceed to the next stage of the EDSP. In this stage, USEPA determines which, if any, of the Tier 2 tests are necessary, based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and to establish a dose-response relationship for the E, A, or T effect.

Between October 2009 and February 2010, USEPA issued test instructions for the first group of 67 chemicals (List 1). A second list of chemicals for EDSP screening was published in June 2013 (List 2). Dimethomorph was not on either of these lists and is currently not yet evaluated for endocrine disruptor effects under the USEPA programme.

Dimethomorph is viewed as an endocrine disruptor for both humans and wild mammals, as non-target organisms, according to points 3.6.5 and 3.8.2 of Annex II to European Commission Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) No 2018/605. EFSA

(2023) did not identify T-mediated endocrine adversity, but a pattern of oestrogen, androgen and steroidogenesis ("EAS")-mediated adversity was observed, which suggested an antiandrogenic mode of action. Requests for derogation were received by the European Commission, and the applicants had submitted evidence regarding the necessity of dimethomorph as a fungicide to control a serious danger to plant health. The European Food Safety Authority ("EFSA") concluded that a derogation was supported for use to combat *Alternaria* disease in potato, one of the crop-pathogen combinations for which SPHINX® EXTRA WG is registered (EFSA 2023).

11 Human incident reports

Dimethomorph incidents were reviewed in 2012 (USEPA 2012). At that time no incidents involving dimethomorph were found in either the Main or Aggregate Incident Data System ("IDS") of the USEPA Office of Pesticide Programs ("OPP") from 1 January 2007 to 13 September 2012. IDS contains reports from across the USA, with most incidents having all relevant product information recorded.

- The Main IDS records incidents resulting in higher severity outcomes (e.g., death, major and moderate incidents), and provides mor case-specific detail.
- Aggregate IDS records incidents resulting in less severe outcomes (e.g., minor, unknown, or no effects).

One low severity case and one moderate severity case were identified in the Sentinel Event Notification System for Occupational Risk ("SENSOR-Pesticides") from 1998 to 2008. The SENSOR pesticide surveillance program and database is administered by the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health ("CDC/NIOSH").

In 2017, USEPA reviewed the OPP IDS for human health incidents involving dimethomorph for the reporting period 2011 to 2016 (USEPA 2018). USEPA (2018) also reviewed the SENSOR-Pesticides database for the reporting period 1998 to 2013.

For the Main IDS from January 1, 2011 to June 23, 2016, there were no reported incidents for the dimethomorph as a single chemical in the database. There was one incident of moderate severity reported involving more than one chemical besides dimethomorph. For Aggregate IDS for same period, there was one incident reported involving dimethomorph, which was classified as of minor severity.

Based on the low frequency and severity of dimethomorph incidents reported to both IDS and SENSOR-Pesticides, there did not appear to be a concern.

12 Ecological risk assessment

12.1 Introduction

A summary of the USEPA's ecological risk assessment is presented in the Interim Registration Review Decision, Case Number 7021 (USEPA 2018). This was based on the comprehensive Ecological Risk Assessment of the Environmental Fate and Ecological Risk of Dimethomorph (USEPA 2016a).

12.2 Terrestrial risks

12.2.1 Introduction

USEPA (2016a) calculated terrestrial wildlife exposure estimates for birds and mammals by focusing on the dietary exposure route of uptake of pesticide active ingredients. These exposures served as surrogates for exposures of terrestrial-phase amphibians and reptiles. For exposures to terrestrial organisms, such as birds and mammals, pesticide residues on food items were estimated on the assumption that organisms were exposed to pesticide residues as a function of the pesticide use pattern.

12.2.2 Risk to mammals

There were no acute risks of concern to mammals. For chronic exposure, dose-based risk quotients ("RQs") ranged up to 5.8, exceeding the Level of Concern ("LOC") (LOC = 1) for mammals of different weight classes foraging in vines treated with 0.224 kg/ha dimethomorph. The results indicate concern for potential chronic risk of adverse effects on reproduction and growth. Effects observed in chronic toxicity studies include decreased body weight gain and percent pup incisor eruption. None of the dietary-based RQs for mammals exceeded the chronic risk LOC, that is, the scenario where mammals are assumed to ingest treated crops (USEPA 2016a).

The potential for adverse effects to mammals from chronic exposure to dimethomorph would be highest for mammals that remain in a site treated at the maximum application rate relevant to grapes, and foraging exclusively on food items containing dimethomorph residues. The likelihood of this scenario is expected to be low. Mammals outside the treated sites are not expected to be adversely affected when exposed to spray drift that moves offsite, as RQs drop below the LOC outside of the treated area. Therefore, considering all factors, the likelihood of adverse effects to mammals from chronic exposure to dimethomorph is assessed as low (USEPA 2016a and 2018).

12.2.3 Risk to birds, reptiles and terrestrial-phase amphibians

The likelihood of adverse effects to birds from acute exposure is anticipated to be low. Results of the USEPA (2016a) ecological risk assessment indicated that birds, terrestrial-phase amphibians and reptiles, were not likely to be adversely affected at a maximum single dimethomorph application rate of 0.224 kg/ha.

Following dimethomorph applications at the maximum single rate of 0.224 kg/ha dimethomorph on crops such as tomatoes, potatoes or grapes, the likelihood of adverse effects to birds from chronic exposure in these application sites is anticipated to be low (USEPA 2016a).

12.2.4 Risk to bees

The USEPA (2016a) evaluated results of the honey bee tests of acute contact and acute oral exposure to dimethomorph. These indicated that dimethomorph is practically nontoxic to young adult honey bees (LD_{50} > 50 µg a.i./bee). No data are available to evaluate toxicity to larval bees or the chronic toxicity to adult bees.

12.2.5 Terrestrial plants

No effects on terrestrial plants were observed at the highest concentration tested at a maximum dimethomorph single application rate of up to 0.45 kg/ha (USEPA 2016a).

12.2.6 Risks to non-target aquatic organisms

Dimethomorph is classified as non-toxic to moderately toxic to aquatic organisms, at concentrations up to the solubility limit. Amphibian-specific data were not available for the USEPA (2016a) evaluation. Using freshwater fish acute toxicity data as a surrogate for aquatic-phase amphibians, the USEPA concluded that dimethomorph would be classified as moderately toxic to aquatic-phase amphibians. Chronic toxicity data for fish and invertebrates showed reproductive effects in estuarine/marine organisms and effects on growth in freshwater organisms. Toxicity data are not available for aquatic non-vascular plants.

Results of the USEPA (2016a) ecological risk assessment indicated that freshwater fish, aquatic-phase amphibians and aquatic invertebrates, were not likely to be adversely affected at a maximum single application rate of 0.224 kg/ha dimethomorph on vines.

Dimethomorph has a low octanol-water partitioning coefficient (K_{ow} = 2.68), which indicates a low likelihood of accumulation in aquatic food chains. As of a result, concerns for risks to piscivorous birds and mammals are not indicated (USEPA 2016a).

12.3 Implications for use and ecological risks in South Africa

The application rate of 0.224 kg/ha dimethomorph, referred to in the above sections, is practically equal to the recommended dimethomorph application rate for SPHINX® EXTRA WG on grapes, which is 0.226 kg/ha. Therefore, it is a valid conclusion that the USEPA (2016a) ecological assessment outcomes presented here are also applicable to dimethomorph in SPHINX® EXTRA WG, applied according to the label instructions in vineyards.

In summary, acute risks are not of concern to mammals and the likelihood of adverse effects from chronic exposure to dimethomorph is assessed as low. The likelihood of adverse effects from acute or chronic exposure to birds, terrestrial-phase amphibians and reptiles is anticipated to be low. Dimethomorph is practically nontoxic to young adult honey bees, but data on larval bees or chronic toxicity to adult bees are not available. No effects are expected on terrestrial plants. Freshwater fish, aquatic-phase amphibians and aquatic invertebrates are not likely to be adversely affected.

13 Ecological incidents

A review of the Ecological Incident Information System ("EIIS") administered by the USEPA's OPP was conducted in April 2016 for the period from 1995 to 2016. No ecological incidents associated with the use of dimethomorph were reported in this source (USEPA 2018).

14 Occupational scenario calculations and results

14.1 Exposure and risk equations

Exposure and risk calculations for occupational handlers are presented in this section, according to the methods and equations used by the USEPA (2016c).

Occupational handler equations

The dermal route of exposure is not calculated for dimethomorph, because dermal exposure does not pose a hazard to health (see Sections 9.7 and 9.8). Inhalation exposure is calculated.

Potential daily exposures are calculated using the following formulas:

$$E = UE * AR * A * 0.001\ mg/ug$$ Equation 14.1.1

where:

E	exposure (mg a.i./day)
EU	unit exposure (µg a.i./kg a.i.)
AR	maximum application rate according to proposed label (kg a.i./ha or kg a.i./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 (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 exposure and risks

As explained in Section 9.12.1, dislodgeable foliar residues, to which post-application workers may be exposed via the dermal route, do not present a hazard to health, since there is no health hazard via the dermal route of exposure (see Sections 9.7 and 9.8). Therefore, equations to conduct a dermal post-application risk assessment for dimethomorph are not required.

Inhalation exposure of post-application workers are considered. Potential inhalation exposure sources include volatilisation of sprayed dimethomorph and resuspension of dusts and/or particulates that contain the fungicide.

A quantitative inhalation exposure assessment for post-application workers was not performed by the USEPA (2015 and 2016c), as explained in Section 9.12.1. It is reasoned that inhalation exposure of mixers/handlers and applicators is likely to result in higher exposure than post-application exposure, and inhalation risks of re-entry workers are assessed relative to the occupational handler (mixer/loader/applicator) as reference risks.

In summary, considering the above information, exposure and risk calculations are not presented for post-application workers.

Summary of terms and values for calculations

A summary of terms and values for the dimethomorph calculations using the above equations is presented in Table 14.1.1.

Table 14.1.1: Summary of terms and values for dimethomorph calculations.

Term	Term symbol	Units	Value
*Unit exposure	UE	µg a.i./kg a.i.	Mixing/loading granules: Inhalation unit exposure = 1.82 (no respirator)
			Applicator, groundboom: Inhalation unit exposure = 0.75 (no respirator)
(Maximum) application rate	AR	kg a.i./litre	0.00023, calculated according to product label (Table 14.3.1)
		kg a.i./ha	0.226 kg/ha (Table 14.3.1)
Area treated or amount handled	A	ha/day	16.2 ha (Table 14.3.1)
Absorption factor	AF	unitless	Inhalation: 100%
Adult body weight	BW	kg	80 (USEPA 2011)
Point of departure	POD	mg/kg-day	Table 9.12.2.1, for different routes and periods of exposure

* Unit exposure: From the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (USEPA 2021b).

14.2 USEPA exposure and risk examples

Occupational handler exposure and risk calculations by the USEPA (2016c) were done only for inhalation exposure, because dermal exposure to dimethomorph does not present a hazard to health. Aerial spraying, spot spraying or backpack spraying is not indicated on the SPHINX® EXTRA WG label, and these examples from USEPA (2016c) are not applicable to SPHINX® EXTRA WG. The USEPA calculated risks associated with spraying of grapes, but only for aerial applications. Therefore, relevant example calculations for the application of SPHINX® EXTRA WG on grapes are not available.

14.3 SPHINX® EXTRA WG calculations and results

Occupational pesticide handlers: mixers, loaders and applicators

The calculation of the spray mixing and application input values needed for the SPHINX® EXTRA WG occupational exposure and risk calculations are presented in Table 14.3.1, and the values of the other equation terms in Table 14.1.1. Data in Table 14.3.1 are as obtained from the product label, and calculated based on the label directions for spray solution preparation (200 g SPHINX® EXTRA WG per 100 litre water).

Exposure calculations according to the USEPA equations described in Section 14.1, performed for occupational pesticide handlers, these are mixers, loaders and applicators, are presented in Table 14.3.2. The product supplier has indicated that the fungicide is not intended for aerial application (e.g., by low-flying aircraft), and spot spraying or backpack spraying is not indicated on the SPHINX® EXTRA WG label; thus, these methods are excluded from the assessment.

As explained previously, dermal exposure to dimethomorph does not present a hazard to health and is not assessed. Completely mechanised applications are highly unlikely to be associated with any significant exposure to workers and are not assessed.

The comparison between the MOEs and the LOCs (Table 14.3.2) indicates the absence of the risk of a health effect in operators involved in mixing, loading and broadcast spraying SPHINX® EXTRA WG on vineyards.

Table 14.3.1: Input values for SPHINX® EXTRA WG dimethomorph exposure and risk calculations for application on grapes (vineyards).

Groundboom broadcast spray					
Label: kg dimethomorph/ kg product	**Label: kg *product/litre spray solution**	**Calculated kg dimethomorph/ litre spray solution**	****Assumed litre solution/ha**	**Calculated kg dimethomorph/ha**	*****Assumed ha treated daily**
0.113	0.002	0.000226	500	0.113	40 acres = 16.2 ha
			1 000	0.226	

*Product: SPHINX® EXTRA WG

**A volume per hectare application rate is not provided on the label, but the conventional range of 500 to 1 000 litre per hectare, to ensure sufficient crop coverage, is assumed.

*** The "area treated daily" for vineyards, using non-aerial application methods, which was used by the USEPA (2016c) to calculate occupational exposures.

Table 14.3.2: Groundboom application in vineyards: occupational handler dimethomorph exposure and MOEs.

AR: maximum application rate (kg dimethomorph/ha)[1]	**Inhalation unit exposure[2] (µg/kg a.i.) [PPE type]**	**Area treated daily[3] (ha)**	**Inhalation exposure**		
			Dose[4] (mg/kg-day)	**LOC = 1 000**	
				MOE	**MOE > LOC?**
Mixer/loader: water dispersible granules for groundboom application - field crop, high hectares					
0.23	1.82 [No-R]	16.2	0.00008	177 180	Yes
Applicator: groundboom broadcast spray					
0.23	0.75 [No-R]	16.2	0.00003	429 910	Yes

Notes to table:
1: Table 14.3.1, calculated from label information.
2: Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (USEPA 2021b). Type of PPE: No-R: No respirator (baseline inhalation PPE).
3: Exposure Science Advisory Council Policy #9.1, field crop high hectares.
4. Algorithms for inhalation dose and MOE calculations presented in Section 14.1.

Post-application (re-entry) agricultural workers are exposed by the dermal route, but dermal exposure to dimethomorph does not present a hazard to health and is not assessed. As explained in Section 14.1, inhalation risks of re-entry workers are assessed relative to the occupational handler as an exposure reference. Given that the dose and MOE calculations presented in Table 14.3.2 did not indicate a risk to handlers, it is concluded that a risk is not indicated for post-application workers, because the inhalation exposure of re-entry workers is expected to be lower than that of handlers.

Non-occupational bystander

As explained in Section 9.13, direct exposure of non-occupational bystanders, that is, inhalation of the spray plume or being sprayed directly, is not likely. Volatilization of pesticides may be a source

of post-application inhalation exposure to individuals nearby pesticide applications and the risks are indirectly assessed by comparison with post-application workers (see Section 9.13).

The dose and MOE calculations presented in Table 14.3.2 did not indicate a risk to handlers, it is concluded that a risk is not indicated for post-application workers, and thus also not to non-occupational bystanders, because their inhalation exposure is expected to be lower.

Spray drift risk assessment

The USEPA (2016c) evaluated incidental oral risks of children aged 1 to 2 years (Section 9.14). Incidental oral risks were calculated for hand-to-mouth ingestion of agricultural spray drift residues deposited on grass. The USEPA risk estimates indicated no risks of concern, based on a dimethomorph groundboom application rate of 0.2 lb/A (0.224 kg/ha) on neighbouring crop fields.

The application rates of dimethomorph relevant to SPHINX® EXTRA WG, namely 0.226 kg/ha for vineyards (Table 14.3.1) is practically equal to the 0.224 kg/ha application rate assessed by the USEPA (2016c).

Since the USEPA did not find a risk for children exposed to dimethomorph deposits on neighbouring grass or lawns, it is concluded that deposits associated with SPHINX® EXTRA WG application rates on grapes would also not present a health risk.

15 Dietary exposure and risk assessment

15.1 Background

Dimethomorph has low acute toxicity by the oral, dermal, or inhalation route of exposure (USEPA 2015). Dietary risk assessment of dimethomorph residues in food is based on its toxicity, on consumer crop intake rates, and on the pesticide residue concentrations in fruits and vegetables at the time of consumption. As discussed in Sections 9.3 and 9.4, the assessment is based on the population-adjusted dose ("PAD"). The acute PAD is referred to as the "aPAD", and the chronic PAD is referred to as the "cPAD". The PAD is equivalent to the POD, the NOAEL, or the LOAEL, divided by applicable uncertainty factors, including the FQPA Safety Factor. For acute and non-cancer chronic exposures, concern is raised when estimated dietary risk exceeds 100 per cent of the aPAD or cPAD, respectively (USEPA 2015).

15.2 Residue intake from food and water

The USEPA (2015) HHRA included acute and chronic dietary (food and drinking water) exposure and risk assessments for all existing dimethomorph uses. Application rates referred to by the USEPA were in the region of 219 to 237 g a.i./ha, which are higher than the rates proposed for dimethomorph (80 to 160 g/ha, Table 14.3.1). An estimated drinking water concentration, based on the highest predicted values for surface and ground water, was calculated by the USEPA (2015). The assessments were "unrefined" (apparently conservative), based on tolerance-level residues, 100 per cent crop treated, and default crop- and food processing factors.

For food and drinking water, the acute dietary risk estimates were below 100 per cent of the aPAD for the general U.S. population (26% of the aPAD) and for all population sub-groups. As expected, the most highly-exposed population subgroup was young children (aged 3 to 5) (39% of the aPAD) at the 95th percentile of exposure. These numbers indicate the absence of concern for children at the higher likely dietary doses.

The chronic exposure estimates were also less than 100 per cent of the cPAD for the general U.S. population (17% of the cPAD) and for all population sub-groups. The most highly-exposed population subgroup was again young children (aged 1 to 2) (26% of the cPAD). Dimethomorph is classified as "not likely to be carcinogenic to humans"; therefore, a cancer dietary risk assessment was not required.

Considering that the dimethomorph application rates proposed for South African agricultural use of SPHINX® EXTRA WG is lower than the rates used by the USEPA (2015), it is concluded that a dietary risk is also not indicated for South African food and drinking water consumers.

16 Summary of conclusions

- SPHINX® EXTRA WG is not intended for sale to residential use; therefore, risks to health, associated with the application of SPHINX® EXTRA WG, are assessed only for the occupational use scenario. The assessment is for application on table and wine grapes, according to label instructions and based on the dimethomorph content indicated on the label.

- The results of the dimethomorph health risk assessment indicated no reasons for concern, including of reproductive/developmental toxicity effects, in agricultural operators handling the product, mixing or applying the product according to the label instructions.

- Dimethomorph is not hazardous through skin contact; therefore, post-application dermal exposure of crop re-entry workers is not associated with a risk to health.

- A risk to health by the inhalation route of exposure, including of reproductive/developmental toxicity effects, is not indicated for post-application workers entering treated crops after spray has dried off, according to SPHINX® EXTRA WG label instructions.

- Volatilisation of pesticides may be a source of post-application inhalation exposure to non-occupational bystanders, that is, individuals nearby pesticide applications. Risks to health, including reproductive/developmental toxicity effects, are not indicated.

- Health risks associated with spray drift is assessed for children, the most sensitive receptors. The assessed scenario is spray drift deposition on nearby grass, where a young child is assumed to play in the grass. Dermal exposure to deposited residues does not pose a risk to health, because dimethomorph is not hazardous by the dermal route of exposure. Incidental oral risks were assessed for hand-to-mouth ingestion of dimethomorph spray drift residues deposited on grass, and the dose ingested in this way is too low to present a risk to health, including of reproductive/developmental effects.

- The risk of a health effect in consumers eating treated crops, and/or drinking water potentially impacted by agricultural applications of SPHINX® EXTRA WG, was examined. A risk to health, including of reproductive/ developmental effects, is not indicated.

- Ecological risks posed by dimethomorph residues on treated crops was assessed for foraging animals and other fauna in contact with residues. Exposed mammals are not at risk due to short-term exposure, and the potential of adverse effects from chronic exposure is low. The likelihood of adverse effects from acute or chronic exposure to birds, terrestrial-phase amphibians and reptiles is anticipated to be low. Dimethomorph is practically nontoxic to young adult honey bees, but data on larval bees or chronic toxicity to adult bees are not

available. Non-target plants are unlikely to be damaged by contact with dimethomorph. Freshwater fish, aquatic-phase amphibians and aquatic invertebrates are not expected to be adversely affected in the agricultural use scenario. These ecological assessments are relevant to the correct use of SPHINX® EXTRA WG, according to label instructions, including label directions to protect the environment.

17 Recommendations

An application for the restricted use of the dimethomorph-containing commercial fungicide SPHINX® EXTRA WG should be granted according to the intended product use:

- Fungicide not for sale to and use by residential gardeners.
- Preparation and application of the treatment solution in accordance with instructions on the product label.
- Personal hygiene instructions on the product label must be followed, that is, washing hands, forearms and face thoroughly after handling chemical products.
- Wearing protective gloves, protective clothing, eye protection and face protection, as directed on the SPHINX® EXTRA WG label, is sufficiently protective if handling and application of the fungicide is according to label instructions.
- Treated crop must not be entered before spray has dried off, according to label instructions.

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