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Toxicological Risk Assessment for the Purpose of Derogation of LINAGAN® SC (L6294) Substance of Concern: Herbicide Molecule Linuron

Report No 026-2024 Rev 1.0

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22 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

22 October 2024

Internal review
Dricky Simpson

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List of Abbreviations

AEL	Acceptable exposure level
AHS	Agricultural Health Study
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	Bioconcentration factor
BEAD	Biological and Economic Analysis Division
CDC	Centers for Disease Control and Prevention
CMR	Carcinogenicity, mutagenicity, and reproductive toxicity
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
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA SF	FQPA Safety Factor
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
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)
TRA	Targeted Risk Assessment
TSCA	Toxic Substances Control Act
TTR	Total toxic residue
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

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 herbicide Linagan® SC, with Act No. 36 of 1947 registration number L6294.

Linagan® SC is identified as a substance of concern due to its classification as a reproductive hazard category 1B (H360Df) according to the Globally Harmonized System of Classification and Labelling of Chemicals ("GHS"). The classification is due to the ingredient linuron, which is classified in GHS as reproductive toxicity category 1B.

Prepared for: ADAMA South Africa (Pty) Ltd
Product name: Linagan® SC
Act No. 36 of 1947 registration number: L6294

Intended product use:
- A suspension concentrate: root- and foliar- absorbed herbicide for the control of weeds in the crops listed or mentioned on the product label.
- The product is for use in large-scale agricultural crop production enterprises.
- Application of the product on small-scale carrot fields, and on small-scale plantings of sweet potato cuttings is allowed, but use on small-scale potato fields is not recommended.
- 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 assessment:
Two occupational designations are assessed:
- Occupational pesticide handlers, exposed by the dermal and inhalation routes of exposure (Table 1).
- Post-application (re-entry) workers are exposed by the dermal route only, since linuron and its residues are not volatile (inhalation exposure to residues on plants is excluded).
- Post-application re-entry of treated post-emergence carrots are restricted as indicated in Table 2.

The product supplier has indicated that the herbicide is not intended for aerial application (e.g., by low-flying aircraft) and this method of application is excluded from the assessment.

Table 1: Occupational pesticide handlers' activities and crops assessment summary.

Pesticide handler activity: Mixing/loading/application			
Application method	**Carrots**	**Potatoes**	**Sweet potato cuttings**
Groundboom, broadcast spray	✔	✔	✔
Backpack, ground/soil-directed or directed on weeds	✔	X	✔

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

The occupational post-application activities indicated in Table 2 are safe with regard to health, and do not involve a risk of reproductive health hazards, provided that specific re-entry periods and personal protective equipment ("PPE") use are adhered to.

Table 2: Safe occupational post-application activities.

Post-application activity and restrictions	Carrots	Potatoes	Sweet potato cuttings
Scouting crops (crop inspection) and weeding by hand, at least 1 day after spraying	✔	✔	✔
Re-entry for hand-setting of irrigation pipes: freshly-planted cuttings sprayed with herbicide, on the day of spraying (label instructions)	Not applicable	Not applicable	✔
Re-entry for hand-setting of irrigation pipes: pre-emergent crops, at least 1 day after spraying	✔	✔	Not applicable
Re-entry for hand-setting of irrigation pipes: post-emergent carrots, within 13 days after spraying: only while wearing a coverall over normal clothing, waterproof gloves and chemically-resistant footwear, e.g., rubber boots	✔	Not applicable	Not applicable

Dietary exposure to treated crops

Human dietary risks of concern are not indicated in the United States Environmental Protective Agency ("USEPA") *Revised Human Health Draft Risk Assessment to Support Registration*, released in 2020. The results of the analysis showed that acute and chronic dietary (food and drinking water) exposure to linuron, and the associated risks, did not exceed safety levels for any US population or population subgroups. It is reasonable to accept that the human dietary risk assessment for linuron will not be different in South Africa.

Health risk assessment results and conclusion

- Levels of linuron to which operators are exposed when mixing and loading Linagan® SC 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 spraying is also not associated with a risk to health.

- Small-scale farming herbicide application by backpack and hand-held wand on crops should be restricted to carrots and sweet potato cuttings, which is not associated with a risk to health. The activity of sequential mixing, loading and backpack application with the required higher herbicide concentration for pre-emergence potatoes is associated with a risk to health (including reproductive health).

- Post-application re-entries after 1 day for the purpose of scouting fields and crops, and for weeding by hand, are not associated with a risk to health (or reproductive effects).

- Post-application re-entry (after 1 day) of pre-emergence carrot and potato fields for the purpose of hand-setting of irrigation pipes, is not of concern with regard to health (or reproductive effects).

- An extended post-application re-entry interval of 13 days is recommended for hand-set irrigation of post-emergence carrots, during which workers should wear coveralls over standard clothing, gloves made of water-resistant material, and chemical-resistant footwear, for which waterproof rubber boots would suffice.

- Sweet potato cuttings are sprayed immediately after planting, and are given light sprinkle irrigation after application to wash herbicide off the leaves of the cuttings (Linagan® SC label instructions). Linuron exposure during hand-setting of irrigation pipes for this purpose is not associated with a risk to health (or reproductive effects), because of the scant crop foliage present at this stage.

Ecological risks

Considering the low frequency and severity of ecological incidents reported in the USA, the USEPA concluded in 2020 that there did not appear to be a concern relating to the use of linuron. This is supported by the following ecological study findings:

- No acute or chronic risks of concern were identified in the aquatic environment.
- No risks of concern were identified for terrestrial invertebrates, including honey bees.
- The crop applications for which registration has been granted are not associated with a risk to birds, reptiles, and terrestrial-phase amphibians.
- No acute risks of concern were identified for mammals.

Restricted use application

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

- Herbicide not for sale to or used by residential gardeners.

- Mixing and application of the treatment solution in accordance with the instructions on the product label.

- Small-scale farmer herbicide application by backpack and hand-held wand on crops should be restricted to carrots and sweet potato cuttings. The activity of sequential mixing, loading and applying with a backpack the required higher herbicide concentration for pre-emergence potatoes is associated with a risk to health. This risk is not applicable to the use of groundboom sprayers.

- Mixing/loading and applying the herbicide with a groundboom is not associated with a risk to health, and also not a risk of reproductive effects, for spraying of carrots (pre- or post-emergence), pre-emergence potatoes or freshly-planted sweet potato cuttings, as described on the product label.

- Personal hygiene instructions on the SDS must be followed; that is, washing hands, forearms and face thoroughly after handling chemical products.

- 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).

- The recommended 1-day post-application restricted-entry interval must lapse before crop re-entry for crop-inspection (scouting) or weeding by hand.

- As indicated on the label, sweet potato cuttings are sprayed immediately after planting, and are given light sprinkle irrigation after application to wash herbicide off the leaves of the cuttings. Exposure to the herbicide during this irrigation practice is not associated with risks to health, because of the scant foliage present at this stage.

- The recommended 1-day post-application restricted-entry interval must lapse before crop re-entry for the purpose of hand-setting of irrigation pipes in sprayed pre-emergence carrot and potato fields.

- In the case of sprayed post-emergence carrots, the restricted-entry interval is 13 days for hand-setting of irrigation pipes. During this period, workers entering the fields for irrigation purposes must wear double-layered clothing, that is, a coverall over basic clothing and water-resistant gloves and shoes (e.g., rubber boots).

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 linuron.

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 provides hazard information for linuron according to the Globally Harmonized System of Classification and Labelling of Chemicals ("GHS").

Section 4 describes essential, concise steps of the health risk assessment paradigm.

Section 5 explains the herbicide action and benefits assessment of linuron.

Section 6 provides an overview of the human health risk assessment methodology.

Section 7 provides a summary and describes the environmental fate assessment for linuron.

Section 8 summarises toxicological reviews for linuron.

Section 9 provides a shorter summary of linuron human dietary risk assessment (food and water).

Section 10 summarises the findings of the US endocrine disruption screening programme.

Section 11 deals with human incident reports.

Section 12 provides information on linuron ecological risk assessment.

Section 13 presents a summary of ecological incidents.

Section 14 summarises conclusions of the INFOTOX review of linuron.

Section 15 presents recommendations following from the INFOTOX study.

Section 16 lists the scientific literature references that were consulted in compiling this document.

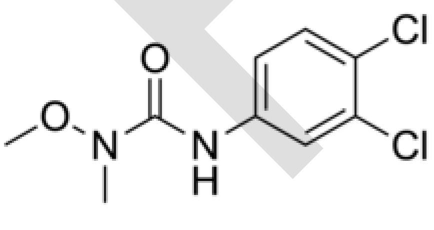
Annexure 1 presents post-application agricultural workers residue transfer coefficients.

3 Hazard identification

3.1 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.

3.2 GHS classification of linuron CAS # 330-55-2



This section summarises the classification of linuron according to the GHS, as presented under the European Chemicals Agency ("ECHA").

As indicated in Table 3.2.1, linuron 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.

Table 3.2.1: GHS classification of linuron, with hazard statement codes, statements, and pictograms.

Hazard class and category code	Hazard Statement Code	Hazard statement	Signal word	Pictogram
Acute Tox. 4	H302	Harmful if swallowed	Warning	
Carc. 2	H351	Suspected of causing cancer	Warning	
STOT RE 2	H373	May cause damage to organs through prolonged or repeated exposure	Warning	
Repr. 1B	H360Df	May damage the unborn child Suspected of damaging fertility	Danger	
Aquatic Acute 1	H400	Very toxic to aquatic life	Warning	
Aquatic Chronic 1	H410	Very toxic to aquatic life with long lasting effects		

Carc. 2 Suspected human carcinogen

- Based on human and animal evidence, but which is not sufficiently convincing to place the substance in Cat 1 (substances known to have a carcinogenic potential for humans based largely on human evidence). Linuron is classified as a USEPA Group C Carcinogen, requiring no quantification of human cancer risk (USEPA 2019). Only substances with Carc. 1 classification fulfil the definition of CMR; therefore, cancer risks of linuron are not assessed in this INFOTOX 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.

4 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/.

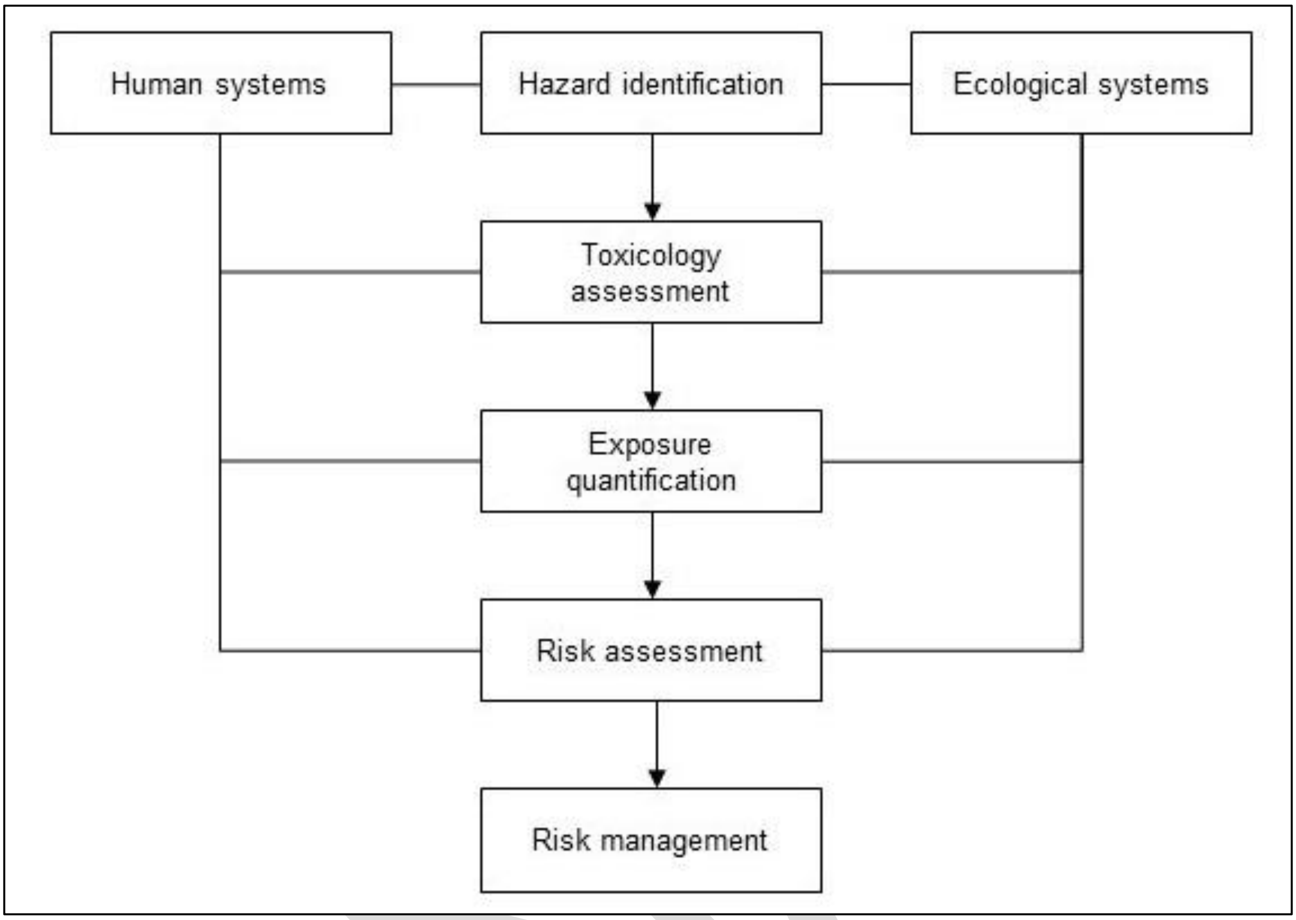


Figure 4.1: The holistic health risk assessment paradigm.

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.

5 Herbicide action and benefits assessment

Linuron (3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea) is a phenyl urea herbicide used to control the growth of grass and weeds in multiple crops. Linuron inhibits electron transport in the photosynthesis process, thereby preventing plant growth and promoting cell membrane destruction. It is registered in the USA and elsewhere as a pre- and post-emergent herbicide. It was first registered in the USA in 1966 (USEPA 1995), and has thus been in use for more than 50 years.

Linuron products are some of the most widely used herbicides in hybrid poplar production in the US. A main benefit of linuron use is that it can be broadcast across the entire field on newly planted or transplanted poplar trees without damage to the crop. Furthermore, linuron can be used in subsequent years, throughout the hybrid poplar growth period.

Linuron also provides high benefits in asparagus production, especially during the post-emergence period when asparagus spears are harvested. It is estimated that asparagus growers could lose up to 15 per cent of net operating revenue (USEPA 2020).

Linuron dominates the market for broadleaf weed control in carrots, and provides timing flexibility as a pre- or post- emergence herbicide. Linuron has a 14-day pre-harvest interval (“PHI”), allowing it to be used later in the season near harvest than other herbicides that have PHIs 30-to-60 days, which is an attractive feature of linuron. It provides timing flexibility, because it can be used as a pre- and post-emergence herbicide to the weed and crop. Because it works on the photosynthesis pathway, it has both soil and leaf activity and can be used either way, depending on the crop and the target weed (USEPA 2018a). It is the preferred herbicide to use when growing carrots.

The Biological and Economic Analysis Division ("BEAD") in the USEPA Office of Pesticide Programs, Science Division, has determined that carrot growers have other broadleaf weed control options, but although linuron is more expensive, it is still dominant in the market, suggesting that the options are inadequate in some way (USEPA 2018a).

6 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 4.1. 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 linuron. This has been discussed in Section 3.2 above.

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

  - INFOTOX retrieved toxicological information from available reproductive/developmental studies and applied 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/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 HRRA focuses on the following occupational exposure scenarios:

- o The dermal and inhalation routes of exposure of herbicide mixers and applicators.
- o The dermal post-application exposure of workers re-entering treated fields.

Residential exposure scenarios are not assessed, because the herbicide assessed with the methodology explained in this report 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 to adults and children to linuron, need not be considered.

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

INFOTOX covered 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 consumers.

- **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.

7 Environmental fate assessment

7.1 Summary

Physical/chemical properties and aspects of environmental fate of linuron are summarised in Table 7.1.1. Unit conversions were made for vapour pressure and Henry's law constant.

Table 7.1.1: Physical/chemical properties of linuron that determine its environmental fate (USEPA 2016a).

Property	Value
Selected physical/chemical parameters	
Molecular weight (g/mol)	249.09
Solubility in water (mg/litre, 25°C)	81
Vapour pressure (Pa)	2.0E-03
Henry's law constant at 25 °C (Pa m^3 mol^{-1})	6.18E-03
Octanol-water partition coefficient (Log K_{OW}),	3.2
Persistence in water	
Hydrolysis half-life (25 ºC)	pH5 = 811days (2.2 years) pH 7 = 1 139 days (3.1 years) pH9 = 1 354 days (3.7 years)
Aqueous photolysis half-life (pH 5)	52 days

Property	Value
Anaerobic aquatic metabolism half-life (25 ºC)	7 days
	16 days
Aerobic aquatic metabolism half-life (days)	41 days (silt loam sediment)
	15 days (sand sediment)
Persistence in soil	
Soil photolysis half-life (13-23 ºC)	96 days
Anaerobic soil metabolism half life	Not listed
Aerobic soil metabolism half-life	52 days (sandy loam) 1 100 days (loam) 171 days (sandy loam) 202 days (sandy clay loam) 127 days (sandy loam)
Mobility	
Soil partition coefficient (K_{OC}) (litre/kg)	Sassafras 1 800 (sandy loam) Traver 2 400 (sandy loam) Tama 1 200 (silt loam) Drummer 2 600 (clay loam)
Soil dissipation	
Terrestrial field dissipation half-lives (days)	20.1 days (sandy loam bare plot) 30.5 days (silty loam bare plot) 100 days (sandy loam soybean plot) 57 days (silty clay loam soybean plot) 10.6 (bare ground) 14 (grapes)
Fish bioconcentration	
Fish bioconcentration factor (BCF)	39x (edible tissues) 240x (non-edible tissues) 49x (whole fish) 92% depuration rate (14 days)

Notes:

1. Sassafras, Traver, Tama and Drummer are names of US soil profiles with typical textures given in brackets in Table 7.1.1 where linuron soil partition coefficients are listed.

2. USEPA (2016a) uses Master Record Identifiers ("MRIDs") to track and manage information submitted to the pesticide program. 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 evaluates 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.

   INFOTOX does not refer to these documents, as there is limited availability of the source publications. Furthermore, the information has gone through USEPA review, and only documents that met the criteria of credible scientific content were retained in the USEPA. USEPA (2016a) is thus presented as the primary reference for ecological risk assessment.

7.2 Environmental fate descriptions

Linuron is soluble in water, and with high K_{OC} values, it may be transported to surface water and groundwater.

Linuron has a low potential to volatilise, considering its vapour pressure (2.0E-03 Pa). Substances with vapour pressure above about 10 Pa at 20 °C are considered volatile.

Furthermore, the calculated Henry's law constant (6.18E-03 Pa m^3/mol) indicates non-volatility from water. Generally, substances with Henry's law constant <1 Pa m^3/mol can be considered non-volatile.

Linuron is relatively stable to hydrolysis (30-day study duration) in water, with half-lives varying from 811 days at pH 5, 1139 days at pH 7 and 1354 days at pH 9 (T=25°C).

Major mechanisms of degradation for linuron include aqueous photolysis, and anaerobic and aerobic aquatic metabolism. Degradation occurs mostly in aquatic environments, due to microbial degradation rather than abiotic hydrolysis.

USEPA (1995) suggested that parent linuron is moderately persistent and relatively immobile in soil. Increased mobility may occur under specific environmental conditions such as in coarse-textured soils and soils with low organic matter content. Linuron dissipates principally by biotic processes such as microbial degradation.

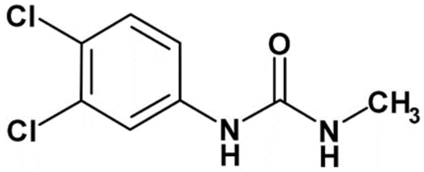
Photodegradation is a potential degradation pathway in aqueous and soil environments. The aqueous photolysis study shows a photo transformation half-life of 52 days whereas the soil photolysis half-life was 96 days calculated from a study conducted for a period of 15 days under continuous irradiation.

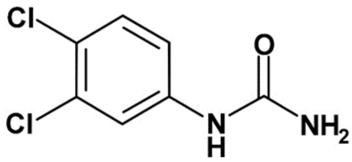
Degradation was more prevalent in aquatic environments (half-lives of 7 to 41 days) than terrestrial environments (half-lives of 52 to 1 100 days).

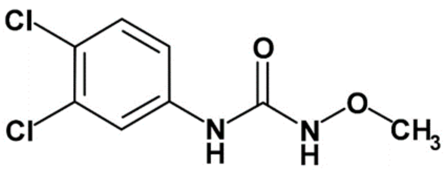
As shown in Table 7.1.1, linuron accumulated in fish with BCFs of 39x, 240x, and 49x in edible tissues, non-edible tissues, and whole fish, respectively. However, 92 per cent of linuron was eliminated from all tissues by day 14 of the depuration period. Based on these data and the chemical log K_{ow} of approximately 3.0, linuron's bioaccumulation potential is indicated as low.

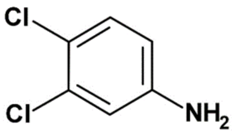
7.3 Degradation

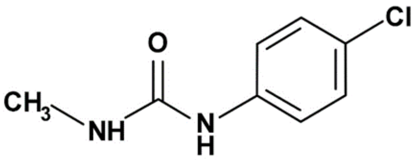
The residues of concern for both enforcement of tolerances and risk assessment in plants and animals are linuron (parent) and its metabolites convertible to 3,4-DCA, including desmethoxylinuron ("DCPMU"), norlinuron ("DCPU"), desmethyl linuron, and hydroxy-norlinuron.

Desmethoxylinuron
3-(3,4-dichlorophenyl)-1-methylurea ("DCPMU")


Norlinuron
N-(3,4-dichlorophenyl)urea (“DCPU”)


Desmethyllinuron
N-(3,4-dichlorophenyl)-N‘-methoxyurea


3,4-Dichloroaniline
3,4-dichlorophenylamine (“3,4-DCA”)


Desmethoxymonolinuron
3 (4-chlorophenyl) 1 -methylurea


The total toxic residue (“TTR”) approach was used in USEPA (2016a), where environmental fate half-lives were re-calculated to account for all residues of concern. Half-lives and Koc values calculated for the residues of concern are listed in Table 7.3.1. The K_{oc} value of desmethoxymonolinuron (“DCPMU”) was used to represent the residues of concern, because it is conservative and forms a prominent portion of the residues of concern.

Table 7.3.1: Environmental fate summary of degradation products of linuron.

Parameter	Value		
Persistence in water			
Hydrolysis half-life (25°C)	pH 5 = 811 days (2.2 years) pH 7 = 1 139 days (3.1 years) pH 9 = 1 354 days (3.7 years)		
Aqueous photolysis half-life (pH 5)	52 days (same as linuron)		
Anaerobic aquatic metabolism half-life (25°C)	Stable 1 068 days		
Aerobic aquatic metabolism half-life (25°C)	698 days (silt loam sediment) 433 days (sand sediment)		
Persistence in Soil			
Soil photolysis half-life (13-23°C)	311 days		
Aerobic soil metabolism half-life (25°C)	177 days (sandy loam) 2 291 days (loam) 1 161 days (sandy loam) 3 384 days (sandy clay loam) 2 006 days (sandy loam)		
Mobility			
Soil partition coefficient (K_{oc}) (litre/kg)	Desmethoxy monolinuron	Desmethoxy linuron	Norlinuron
Sassafras (sandy loam) Traver (sandy loam) Tama (silt loam) Drummer (clay loam)	1 000 520 710 1 100	6 100 4 500 3 900 8 100	2 400 3 800 4 100 10 000
Mean K_{oc} =	833	5 650	5 075
Source: (USEPA 2016a)			

3,4-DCA is not of regulatory concern in connection with the registered uses of linuron due to the very low levels at which it is detected in plants and animals (<0.01ppm) (USEPA 2016a).

Toxicity data have not been submitted for degradation products of linuron, but metabolites convertible to 3,4-DCA are not likely to be more toxic than the parent compound (USEPA 2016a).

Therefore, risk assessments for linuron are expected to be protective for any toxicity arising from degradation products of the parent compound.

8 Toxicological reviews

8.1 Introduction

USEPA (2019) (*Revised Human Health Draft Risk Assessment to Support Registration Review*) referred to USEPA (2016b) (*Human Health Draft Risk Assessment for Registration Review*) for toxicological reviews of linuron.

8.2 Toxicological effects

Following repeated oral dosing in test animals, linuron was found to produce three primary effects (USEPA 2016b):

- Changes in the haematopoietic system in dogs, rats, and mice;
- Changes in the male reproductive system in developing rats; and
- Decreases in triiodothyronine (T3) and thyroxine (T4) levels detected in blood tests in the Endocrine Disruptor Screening Program ("EDSP") Tier 1 screening assays in rats.

USEPA (2016b) conducted a literature search to assist in informing the linuron hazard assessment. An initial screen of published literature was conducted on Google and Web of Science. Subsequently, the search was expanded to include Pub Med, Toxline, National Library of Medicine, ToxNet, the Agency for Toxic Substances and Disease Registry ("ATSDR") toxicity profiles, and the European Food Safety Authority ("EFSA"). Several publications were found that provided relevant hazard information on the reproductive and developmental effects observed in guideline studies. The publications were discussed in USEPA (2016b) and details are not repeated in this INFOTOX report. USEPA (2019) assessed the studies as to be of good quality and provided sufficient information to assess whether linuron poses a human health hazard. The only amendment was to the FQPA safety factor of 10x because of incomplete information in the EDSP assessment at the time, as discussed below.

EDSP recommended that a comparative thyroid assay in pregnant, foetal, postnatal, and non-pregnant adult rats be conducted to address the concern for the potential of linuron to influence thyroid levels in pregnant females, and potentially the foetus or newborn. In the interim, a FQPA safety factor of 10x was applied for linuron (USEPA 2016b).

In the USEPA (2019) assessment, the selected toxicity endpoints and PODs were based on effects observed from the currently available database for linuron. The toxicology and exposure data had been evaluated and linuron was determined to be safe for infants and children, supporting the reduction of the FQPA safety factor to 1x.

A summary of toxicological doses and endpoints for linuron for application in dietary and occupational human health risk assessments is presented in Table 8.2.1 (USEPA 2019).

Table 8.2.1: Summary of toxicological doses and endpoints for linuron for application in dietary and occupational human health risk assessments (USEPA 2019).

Point of departure (POD)	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for risk assessment	Study and toxicological effects
Acute dietary (general population, including infants and children)			
NOAEL = 20 mg/kg-day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Acute RfD = 0.2 mg/kg-day aPAD = 0.2 mg/kg-day	Acute neurotoxicity study (rat). LOAEL = 100 mg/kg-day based on decreases in rearing and in motor activity.
Acute dietary (females 13-49 years of age)			
NOAEL = 12 mg/kg-day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Acute RfD = 0.12 mg/kg-day aPAD = 0.12 mg/kg-day	Rat developmental toxicity. LOAEL = 50 mg/kg-day based on increased post-implantation loss and foetal/litter resorptions.
Chronic dietary (all populations)			
NOAEL = 0.77 mg/kg-day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Chronic RfD = 0.0077 mg/kg-day cPAD = 0.0077 mg/kg-day	1-year dog study. LOAEL = 3.5 mg/kg-day based on haematological effects (increased met- and sulf-haemoglobin levels).
Incidental oral short term (1 to 30 days)			
NOAEL = 0.77 mg/kg-day	UF_A=10× UF_H=10× FQPA SF/UF_{DB} = 1×	Non-occupational spray drift LOC for MOE <100	Co-critical: 1-year oral dog study and 2-generation reproduction rat study Dog: LOAEL = 3.5 mg/kg-day based on haematological effects (increased met- and sulf-haemoglobin levels) Rat: offspring LOAEL = 5.8 mg/kg-day based on decreased pup weight
Dermal short-term (1 to 30 days)			
NOAEL = 0.77 mg/kg-day	UF_A=10× UF_H=10× FQPA SF/ UFDB = 1×	Non-occupational spray drift LOC for MOE < 100 Occupational LOC for MOE < 100	Co-critical: 1-year oral dog study and 2-generation reproduction rat study Dog: LOAEL = 3.5 mg/kg-day based on haematological effects (increased met- and sulf-haemoglobin levels). Rat: offspring LOAEL = 5.8 mg/kg-day based on decreased pup weight
Inhalation short-term (1 to 30 days)			
NOAEL = 0.77 mg/kg-day	UF_A=10× UF_H=10× FQPA SF/UF_{DB} = 1×	Occupational LOC for MOE < 100	Co-critical: 1-year oral dog study and 2-generation reproduction Rat study Dog: LOAEL = 3.5 mg/kg/day based on haematological effects (increased met- and sulf-haemoglobin levels). Rat: offspring LOAEL = 5.8 mg/kg-day based decreased pup weight

Point of departure (POD)	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for risk assessment	Study and toxicological effects
Cancer (oral, dermal, inhalation)			
Classification: USEPA Group C Carcinogen requiring no quantification of human cancer risk			

Point of Departure (POD) = A data point or an estimated point that is 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. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Assumptions:
The dermal absorption factor of 6 per cent should be applied to extrapolate from the oral route to the dermal route.
A default 100 per cent absorption rate should be used to extrapolate from the oral route to the inhalation route.

9 Human dietary risk assessment

Human dietary risks of concern are not indicated in the *Revised Human Health Draft Risk Assessment to Support Registration* (USEPA 2019). The results of the analysis showed that acute and chronic dietary (food and drinking water) exposure and risks did not exceed the respective LOCs for the US population and all population subgroups.

It is reasonable to accept that the human dietary risk assessment for linuron will not be different in South Africa.

10 Endocrine disruptor screening programme

As required by the US Federal Food, Drug, and Cosmetic Act ("FFDCA"), linuron is subject to the endocrine screening part of the Endocrine Disruptor Screening Program ("EDSP") of the USA.

USEPA has developed the EDSP "*to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid ("E", "A", or "T") hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine 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 establish a dose-response relationship between the dose and the E, A, or T effect*".

Between October 2009 and February 2010, USEPA initiated testing of the first group of 67 chemicals under the EDSP, which included 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013, and included some pesticides scheduled for registration review, and chemicals detected in water. Linuron was on the first list, for which USEPA received all of the required Tier 1 assay data. There was insufficient evidence to classify linuron as an endocrine disruptor (USEPA 2019).

11 Human incident reports

USEPA (2019) summarised findings recorded in the Office of Pesticide Programs ("OPP") Incident Data System ("IDS") and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health ("CDC/NIOSH") Sentinel Event Notification System for Occupational Risk-Pesticides ("SENSOR") databases for pesticide incident data on the active ingredient linuron. From January 1, 2010 to December 3, 2015, there were no incidents reported to the IDS involving linuron. One previous case, which occurred in 2009 in California, was classified as of moderate severity. The case involved an agricultural worker who was affected while laying a pipeline in a carrot field that had been sprayed with linuron. The worker experienced respiratory symptoms, including cough, upper respiratory pain, and pleuritic chest pain (pain on deep breathing).

In addition, findings from the US Agricultural Health Study ("AHS") were reviewed (USEPA 2019). Scientists investigated the occurrence of bladder cancer in enrolled AHS participants. Cancer incidence information was obtained from cancer registries in Iowa and North Carolina for all incident bladder cancers diagnosed from 1993-to-1997. In total, 321 cases of bladder cancer were diagnosed among male applicators. Among those participants that reported "ever using" linuron, the investigator found no association with bladder cancer.

12 Ecological risk assessment

12.1 Introduction

USEPA's review of potential ecological risks associated with linuron is summarised in USEPA (2020).

The point of departure was the *Preliminary Ecological Risk Assessment for Registration Review* (USEPA 2016a), amended following the release of the *Response to Comments on the Preliminary Ecological Risk and Drinking Water Assessments to Support Registration Review* (USEPA 2018b), and *Addendum to Ecological Risk Assessment in Support of Registration* (USEPA 2018c).

12.2 Terrestrial Risks

12.2.1 Mammals

USEPA (2020) did not identify any acute risks of concern for mammals. Potential chronic risks for mammals were identified for all application scenarios based on the maximum application rates on current labels. The highest risk quotients ("RQs") were from the use of linuron on hybrid poplar at the currently labelled maximum seasonal application rate. The chronic endpoint for mammals is based on decreased pup weight and survival.

12.2.2 Birds, reptiles, and terrestrial-phase amphibians

Potential acute dose-based risks of concern for birds were identified, with based on the use of linuron on hybrid poplar at the currently labelled maximum rate. However, after considering the new lower application rates for hybrid poplar, there are no longer acute risk concerns for birds from this use. The next highest acute RQs were based on the linuron uses on non-crop areas, which were no longer registered use sites. For the remaining use scenarios with acute risk estimates of concern, RQs were only above the LOC for small birds eating short grass. Since small birds are unlikely to consume a diet consisting of only or mostly short grass, this scenario is not regarded as of concern.

12.2.3 Terrestrial invertebrates (honey bees)

No risks of concern were identified for terrestrial invertebrates based on the available honey bee acute contact toxicity data for linuron. However, honey bee oral toxicity data were not available for linuron (USEPA 2020).

Additional data may be necessary to fully evaluate risks to non-target terrestrial invertebrates, especially pollinators.

12.2.4 Terrestrial plants

Potential risks to non-target terrestrial plants, including monocots (grass and grass-like flowering plants) and dicots (angiospermous plant such as a deciduous tree or broad-leaved herb), were identified in both mountainous and semi-aquatic habitats (USEPA 2020). RQs based on exposure to spray drift range from 0.2 to 2.1 for terrestrial plants. The highest RQs for dicots were based on the use of linuron on non-crop areas, post-harvest areas, crop stubble, fallow ground, and stale seedbeds at the current maximum single application rate. However, USEPA (2020) observed that these uses were to be deleted.

The next highest RQs for dicots were based on the use of linuron on hybrid poplar at the current maximum single application rate. Since the hybrid poplar application rate was to be reduced, RQs at the lower rate would only slightly exceed the LOC for the most sensitive species tested.

12.3 Aquatic risks

12.3.1 Freshwater fish and aquatic-phase amphibians

No acute risks of concern were identified for freshwater fish or aquatic-phase amphibians (USEPA 2020).

Potential chronic risks to freshwater fish were identified for carrots, hybrid poplar, and some herbs. The chronic endpoint for freshwater fish is based on inhibition of growth. There is some uncertainty regarding chronic risks to freshwater fish, as the growth effects were seen at the lowest dose tested in the linuron toxicity test. A more sensitive endpoint value was used from the herbicide, diuron, regarded as a similar herbicide, but it is not clear whether linuron would be as toxic to aquatic animals as diuron.

12.3.2 Estuarine/marine fish and estuarine/marine invertebrates

No acute or chronic risks of concern associated with linuron applications in the agricultural industry were identified for estuarine/marine fish and invertebrates (USEPA 2020).

12.3.3 Freshwater invertebrates

No acute risks of concern were identified for freshwater invertebrates. Potential chronic risks to benthic freshwater invertebrates were identified from all uses of linuron, including uses with currently-labelled maximum single application rates (USEPA 2020). However, RQs ranged from 0.69 to 3.0, which do not indicate excessive risks.

12.3.4 Aquatic vascular and non-vascular plants

Potential risks of concern were identified for aquatic vascular and non-vascular plants. The endpoint for aquatic vascular plants is based on inhibition of growth, for which RQs ranged from 0.40 to 2.0. For non-vascular plants, RQs ranged from 0.78 to 3.8. The RQs do not indicate excessive risks.

13 Ecological incidents

The US Ecological Incident Information System ("EIIS") under the Office of Pesticide Programs ("OPP"), was used to identify ecological incidents associated with the use of linuron and exposure to major degradation products. Incidents in this database constitute of those that have been investigated, linked to one or more pesticide active ingredients, and reported to the Office of Pesticide Programs. A review of the EIIS database for incidents involving linuron was completed on 8/27/15. Incidents in this system are categorised by "certainty", that is, the certainty that linuron was the cause of the observed effects.

In addition to the incidents recorded in EIIS, additional incidents are reported to the OPP in aggregated form. Ecological incidents reported in aggregate reports include those categorised as "*minor fish and wildlife"*, "*minor plant"*, and "*other non-target* incidents". *Other non-target incidents* include reports of adverse effects to insects and other terrestrial invertebrates. A total of nine incidents were reported in the database. Six of these affected plants, and five were caused by incidental contact through spray drift, primarily to trees. Six incidents were categorised with a certainty level of "*possible*" and three incidents with a certainty level of "*probable*". Only three incidents were the result of registered use of linuron, while five incidents were the result of accidental misuse and one the result of intentional misuse.

The Avian Incident Monitoring System ('AIMS") maintained by the American Bird Conservancy, was searched on November 5, 2015 and no ecological incidents had been recorded resulting from the use of linuron (USEPA 2016a).

USEPA (2016a) pointed out that some incidents may go unreported since effects may not be immediately apparent, or may not readily be attributed to the use of linuron. Consequently, the absence of incident reports may not be construed as an absence of incidents. An updated search of the EIIS in June, 2019, did not identify new linuron incidents reported to the database since the previous search.

Considering the low frequency and severity of ecological incidents reported in EIIS, AIMS, and in aggregated form, USEPA (2020) concluded that there did not appear to be a concern relating to the use of linuron.

14 Occupational exposure calculations

14.1 Exposure and risk equations

Risk assessment example calculations for occupational handler and post-application workers are presented in this section. USEPA examples results for occupational handlers are presented in Section 14.2. Example results for worker exposure and risk calculations in crops targeted in South Africa, namely carrots, potatoes and sweet potatoes were also performed by the USEPA (2016c and 2019).

Occupational handler equations

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 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 (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 equations

Potential daily exposures for occupational post-application workers are calculated by the USEPA (2016c) 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 foliage residue on day "t" (µg/cm^2)
AR	application rate (lb a.i./A)
F	fraction of a.i. 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:

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

where:

DFR_t	dislodgeable foliage residue on day "t" ($\mu g/cm^2$)
AR	application rate (kg a.i./ha)
F	fraction of a.i. 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" ($\mu g/cm^2$)
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 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 a.i./kg-day)
E	exposure (mg a.i./day)
AF	absorption factor (dermal and/or inhalation)
BW	body weight (kg)

The MOE is calculated with Equation 14.1.3.

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

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

Table 14.1.1: Summary of terms and values for calculations.

Term	Term symbol	Units	Value
Unit exposure	UE	µg a.i./kg a.i.	Tables 14.2.1
(Maximum) application rate	AR	kg a.i./ha or kg a.i./litre	According to product label
Area treated or amount handled	A	ha/day or litre/day	Default values in Table 14.2.1
Absorption factor	AF	unitless	Dermal: 6% Inhalation: 100%
Adult body weight	BW	kg	80 (USEPA 2011)

Term	Term symbol	Units	Value
Point of departure	POD	mg/kg-day	Table 8.2.1, for different routes of exposure
Fraction of a.i. retained on foliage	F	unitless	Carrots post-emergence: 0.25 (25%, default) Potatoes pre-emergence: 0.10 (10%, weeds only, maximum size 2- to 5 leaves) Sweet potato cuttings: 0.058 (5.8%)
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
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.

* Linagan® SC 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.

14.2 USEPA exposure and risk examples

Occupational handler example exposure and risk assessment data and results (USEPA 2016c), using the equations presented in Section 14.1, are summarised in Table 14.2.1. Amongst the application methods for which calculations are illustrated by the USEPA (2016c), only the groundboom application is applicable to Linagan® SC; therefore, only groundboom application example calculations are presented in Table 14.2.1. The USEPA example calculation MOEs for *Mixing/loading liquid*, for *groundboom application* in a *field crop, typical hectares*, indicated in bold type in Table 14.2.1, is lower than the LOC of 100. Note that the USEPA (2016c) had used an LOC of 1 000, which was corrected to 100 in USEPA (2019). The LOC of 100 is used for comparison in Table 14.2.1.

Table 14.2.1: USEPA example of linuron occupational handlers' exposure doses and MOEs.

Exposure scenario	Crop or Target[1]	Unit exposure[2] (µg/kg a.i.) [PPE types]		Maximum App. Rate[3] (kg a.i./ha or kg a.i./litre)	Area treated daily[4]	Dermal[5]		Inhalation[6]	
		Dermal	Inhalation			Dose (mg/kg-day)	MOE LOC=100	Dose (mg/kg-day)	MOE LOC=100
Mixing/loading liquid for groundboom application	Field crop, typical hectares	64.2 [DL/G]	0.48 [No-R]	-	32.4 ha	0.00303	250	0.00038	2 000
	Field crop, high hectares				80.9 ha	0.0089	**87**	0.0011	690
Applying sprays with groundboom	Field crop, typical hectares	35.5 [SL/G]	0.75 [No-R]	-	32.4 ha	0.017	460	0.0059	1 300
	Field crop, high hectare				80.9 ha	0.0049	140	0.0017	450

Notes to table:

1. Typical hectares field crops include carrots (USEPA 2016c).
   High hectares field crops include expanded use on tuberous vegetables (potatoes and sweet potatoes) (USEPA 2016c).
2. Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (USEPA 2015a, superseded by USEPA 2021).
   Type of PPE: SL/G: Single layer clothes (baseline attire) with gloves.
   DL/G: Double layer clothes with gloves and rubber boots.
   No-R: No respirator (baseline inhalation PPE)
3. "-": value not provided, but calculations with maximum application rates are indicated in USEPA (2016c) and doses and MOEs calculated by the USEPA are presented here.
4. Exposure Science Advisory Council Policy #9.1.

5 and 6. Algorithms for dermal and inhalation dose and MOE calculations are presented in Section 14.2.

14.3 Proposed Linigan SC use pattern and exposure profile

Crops and spray application methods

A summary of crops and spray application methods are presented in Table 14.3.1, as summarised from the Linagan® SC label.

Table 14.3.1: Linagan® SC crop and spray application matrix.

Crop		Carrots		Potatoes		Sweet potato cuttings	
Market	Farming: large- or small-scale	**Large-scale**	**Small-scale**	**Large-scale**	**Small-scale**	**Large-scale**	**Small-scale**
Application method	Groundboom	✓	N.a	✓	N.a	✓	N.a
	Backpack with handheld sprayer, with or without compressor pump	N.a	✓	N.a	N.a	N.a	N.a
Assumed hectares	Small-scale farmer	N.a	✓	N.a	✓	N.a	✓
	Field crop, typical hectares	✓	N.a	✓	N.a	✓	N.a
	Field crop, high hectare	✓	N.a	✓	N.a	✓	N.a

N.a.: Not applicable

The product supplier has indicated that the herbicide is not intended for aerial application (e.g., by low-flying aircraft) and this method of application is excluded from the assessment.

The areas to be treated (hectares) are the default areas recommended by the USEPA (2016c) and presented in Table 14.4.1. Three default area categories are used by the USEPA, namely:

- Ornamental crops and cut flowers (40 acres = 16.2 ha).
- Field crop, typical hectares (80 acres = 32.4 ha).
- Field crop, high hectares (200 acres = 80.9 ha).

It is expected that mostly large-scale or commercial farmers will use the product, and that these users will not use backpacks as an application method. Small-scale farmers might use backpacks, but these are not to be confused with residential gardens, since the product will not be available to residential gardeners. The use of backpacks by small-scale farmers are 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 farming applications of Linagan® SC. The USEPA (2015b) described handgun applications as sprayed with a handheld wand/hose/nozzle attached to vehicle-mounted mechanical pressurizing pump and large spray tank. This is not the same as the mechanically pressurised backpacks illustrated in Figure 14.3.1. However, reference is made to handgun applications, to put in perspective the scale of values chosen for calculations for small-scale farmers, using backpacks, in this report.

Two types of backpack sprayers are available in South Africa, namely, a backpack with a handheld sprayer, which is not mechanically-pressurized (Figure 14.3.1(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 14.3.1(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.

(b) Not mechanically pressurised

(a) Mechanically pressurised

Source: Foqué (2012)

Figure 14.3.1: Backpack sprayers available in South Africa.

The reported spraying time (USEPA 2015b) with backpacks 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). Handgun times ranged from 3.3 to 11.4 hours, and the area sprayed on a work day from less than 1 to approximately 20 acres (less than 0.4 to 8.1 ha). It appears that the maximum area that can be sprayed on foot with a backpack in one work day is approximately 2.4 ha.

Personal Protective Equipment ("PPE")

PPE-use recommended on the product label includes tightly sealing safety goggles, suitable protective clothing, gloves and boots protecting against harmful chemicals, and/or 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] in Table 14.4.1. Use of respiratory protection is recommended on the Linagan® SC label only in case of insufficient ventilation, perhaps as applicable to tunnel farming, and thus assumed unlikely for agricultural workers working in the open.

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 1 day is assumed, which is usual for herbicide products.

Occupational exposure profile

The occupational exposure profile is summarised in Table 14.3.2.

Table 14.3.2: 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

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 summarized in Table 14.4.1 to 14.4.3.

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). Such 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 (USEPA 2016c and 2019).

The expected exposure scenarios and the quantitative exposure/risk assessment matrix developed for occupational post-application workers are summarized in Table 14.4.4.

14.4 Linagan® SC calculations

The calculation of the spray application input values needed for the Linagan® SC occupational exposure and risk calculations are presented in Table 14.4.1. 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 Tables 14.4.2 to 14.4.3.

Dermal and inhalation PODs are based on the same toxicological endpoints (see Table 8.2.1) and doses determined for these routes can be combined to calculate a combined (total) MOE, presented in Tables 14.4.4 and 14.4.5, using Equation 14.4.1 (USEPA 2019):

Total MOE = [NOAEL (mg/kg-day)] ÷ [(Dermal Dose + Inhalation Dose) (mg/kg-day)]

Equation 14.4.1

where:
The NOAEL = 0.77 mg/kg-day (Table 8.2.1).

Post-application (re-entry) agricultural workers are exposed by the dermal route only, since linuron and its residues are not volatile (inhalation exposure is excluded).

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.

Re-entry exposure is assessed according to the crop types indicated on the Linagan® SC label. Re-entry exposure and risk results are presented in Table 14.4.6.

Linagan® SC is a herbicide, with the following application instructions according to the product label:

- Carrots: pre- and post-emergence
- Potatoes: pre-emergence only: "May be sprayed after planting until prior to emergence of first leaves of crop."
- Sweet potato cuttings: "Apply immediately after transplanting before active growth starts.
-
- Give light sprinkle irrigation after application to wash herbicide off the leaves of the cuttings".

These application instructions have a direct effect on the likelihood of post-application re-entry exposure of agricultural workers:

- Carrots: pre- and post-emergence: possible foliar contact with treated weeds and/or carrot leaves in the 4-leaf- or more growth stage for all assessed activities.
- Potatoes: pre-emergence only: foliar contact with treated weeds. The fraction of active ingredient retained on weed foliage is assumed to be 10% (not the default of 25% used for post-application dislodgeable foliar residue ("DFR") calculations) (Table 14.4.3).
- Sweet potato cuttings:
    - According to a Department of Agriculture undated brochure on sweet potatoes, approximately 14 500 shoots are planted per ha.
    - The instruction is that each shoot should have 4 leaves attached at most. The estimated foliar area of 4 leaves is (20 x 20 cm = 400 cm^2). The total foliar coverage of 1 ha planted with shoots is thus (400 cm^2 x 14 500 shoots = 5.8 x 10^6 cm^2).
    - Assuming that shoots are planted in fields practically free of weeds on the day of planting, the foliar area available for herbicide interception on the day of planting is approximately (5.8 x 10^6 cm^2), that is (5.8 x 10^6 cm^2 x 10^{-8} cm^2/ha = 0.058 ha). Thus, the fraction of active ingredient retained on foliage should not be more than 5.8% and the default fraction of 25% used for post-application DFR calculations an overestimation in the case of sweet potato cuttings (Table 14.4.3).
    - It is assumed that the "*light sprinkle irrigation*" necessitates irrigation within an hour or two after application, that is, the re-entry time in the case of hand-setting of irrigation pipes is 0 days (Table 14.4.3).

The assessed re-entry activities are:

- Irrigation, hand setting of pipes.
- Scouting, that is, inspecting of crops.
- Weeding by hand. This is unlikely for large farms, but assessed because small-scale farmers might also use the product.

Table 14.4.1: Crop-specific spray input values for Linagan® SC exposure and risk calculations.

Crop	Groundboom spray			
	Label: kg linuron/litre product	Label: litre product/ha, maximum	Calculated maximum kg linuron/ha	Hectares sprayed per day
Carrots	0.5	2.0	1.0	32.4 ha - field crop, typical hectares
Potatoes	0.5	3.0	1.5	80.9 ha – field crop, high hectares
Sweet potatoes cuttings	0.5	2.0	1.0	
Backpack spray				
Crop	**Label: minimum litre solution/ha**	**Litre solution handled/day**	**Calculated maximum kg linuron/litre solution**	**Hectares sprayed per day (per applicator)**
Carrots	300	340	0.003	1.1 ha
Potatoes	300	340	0.005	
Sweet potatoes cuttings	300	340	0.003	

Notes to Groundboom spray:
Hectares sprayed per day are the USEPA default values, see Table 14.2.1.
Notes to Backpack spray:
Label: minimum litre solution/ha is the minimum volume solution/ha recommended on the label. The minimum volume is associated with the maximum concentration of linuron per litre solution handled by the backpack spray mixer/loader/applicator.
Litre solution handled per day is motivated in Section 14.3.
Calculated maximum kg linuron/litre solution is the maximum kg linuron/ha (groundboom) * litre solution/ha.
The Linagan® SC label does not indicate a different application rate for the use of a backpack instead of a groundboom sprayer.
Hectares sprayed per day is calculated as (litre solution handled/day) / (label: minimum litre solution/ha)

Table 14.4.2: Unit exposure values for Linagan® SC exposure and risk calculations.

Spray parameters		[1]Unit exposure (µg/kg a.i.) [PPE types]	
		Route of exposure	
		Dermal	Inhalation
Groundboom broadcast spray	Mixing/loading liquid for groundboom application	64.2 [DL/G]	0.48 [No-R]
	Applying spray with groundboom	27.8 [DL/G]	0.75 [No-R]
Backpack spray	Mixing/loading/application	9 084.6 [DL/G]	5.69 [No-R]

[1] Based on the updated “Occupational Pesticide Handler Unit Exposure Surrogate Reference Table” (USEPA 2021).
Type of PPE: DL/G: Double layer clothes with gloves.
No-R: No respirator (baseline inhalation PPE)

Unit exposure values are used to calculate the exposure of pesticide operators mixing/loading/spraying the product (Equation 14.1.1).

Table 14.4.3: Fraction of linuron retained on foliage (crop and/or weeds), crop- and activity-specific REIs.

Crop	Fraction linuron retained on foliage (default = 25%)	Post-application activity	REI used for dose calculation
Carrots	Post-emergence: 25%	Irrigation (hand-set)	See Table 14.4.6
		Scouting or weeding by hand	1 day
	Pre-emergence: 10%	Irrigation (hand-set)	See Table 14.4.6
Potatoes	10%	Irrigation (hand-set)	See Table 14.4.6
		Scouting or weeding by hand	1 day
Sweet potatoes cuttings	5.8%	Irrigation (hand-set)	0 days
		Scouting or weeding by hand	1 day
Values are used to calculate the dislodgeable foliar residue (DFR) at the time of re-entry (Equation 14.1.4).			

Table 14.4.4: Groundboom application: occupational handler exposure and MOEs.

Crop	AR: Maximum Application Rate (kg/ha)	Dermal exposure			Inhalation exposure			Total exposure		
		Dose (mg/kg-day)	LOC = 100		Dose (mg/kg-day)	LOC = 100		Dose (mg/kg-day)	LOC = 100	
			MOE	MOE > LOC?		MOE	MOE > LOC?		MOE	MOE > LOC?
Mixer / loader: Liquid, groundboom, broadcast										
Carrots	1.0	0.0016	494	Yes	0.00020	3 940	Yes	0.00175	439	Yes
Potatoes	1.5	0.0058	132	Yes	0.00073	1 051	Yes	0.00658	117	Yes
Sweet potatoes cuttings	1.0	0.0039	198	Yes	0.00049	1 576	Yes	0.00438	176	Yes
Applicator: Groundboom broadcast spray										
Carrots	1.0	0.0009	893	Yes	0.00030	2 538	Yes	0.00117	661	Yes
Potatoes	1.5	0.0032	238	Yes	0.00114	677	Yes	0.00437	176	Yes
Sweet potatoes cuttings	1.0	0.0022	357	Yes	0.00076	1 015	Yes	0.00291	264	Yes

Notes to table:
AR: Maximum Application Rate is the *Calculated kg linuron / ha, maximum* in Table 14.4.1.

Table 14.4.5: Backpack application: occupational handler exposure and MOEs.

Crop	Linuron concentration in spray solution (kg linuron/litre solution)	Dermal exposure			Inhalation exposure			Total exposure		
		Dose (mg/kg-day)	LOC = 100		Dose (mg/kg-day)	LOC = 100		Dose (mg/kg-day)	LOC = 100	
			MOE	MOE > LOC?		MOE	MOE > LOC?		MOE	MOE > LOC?
Mixer / loader / applicator: Liquid, backpack, ground/soil-directed.										
Carrots	0.003	0.0069	110.80	Yes	0.00007	10 616	Yes	0.00702	110	Yes
Potatoes	0.005	0.0116	66.48	No	0.00012	6 369	Yes	0.01170	66	No
Sweet potatoes cuttings	0.003	0.0069	110.80	Yes	0.00007	10 616	Yes	0.00702	110	Yes

Notes to table:
Linuron concentration in spray solution is the *Calculated kg linuron / litre solution* in Table 14.4.1.

Table 14.4.6: Post-application exposure and risks.

Activity	AR: Maximum App. Rate	Dermal			
		Dislodgeable foliar residue at time of entry	Dose	LOC = 100	
	kg/ha	DFR_t (µg/cm^2)	(mg/kg-day)	MOE	MOE > LOC?
Scouting, all REIs = 1 day					
Carrots (post-emergence)	1.0	2.250	0.00284	272	Yes
Potatoes	1.5	3.375	0.00425	181	Yes
Sweet potato cuttings	1.0	2.372	0.00095	815	Yes
Weeding by hand, all REIs = 1 day					
Carrots (post-emergence)	1.0	2.250	0.00095	815	Yes
Potatoes	1.5	3.375	0.00142	543	Yes
Sweet potato cuttings	1.0	2.250	0.00311	248	Yes
Irrigation, hand set. **USEPA (2021) foliar-to-skin TCs used for these calculations are based on standard clothing worn by agricultural field workers: shoes, socks, long-legged pants, and long-sleeved shirts. No coveralls and no gloves are assumed.**					
Irrigation, hand set: <u>Carrots, pre-emergence</u>. **Assumed scant weed infestation. Assumed fraction of sprayed linuron retained = 10% (Table 14.4.3).**					
REI = 2 days	1.0	0.810	0.00923	83	No
REI = 3 days	1.0	0.729	0.00831	93	No
REI = 4 days	1.0	0.656	0.00748	103	Yes
Irrigation, hand set: <u>Carrots, post-emergence.</u> **Assumed fraction of sprayed linuron retained = USEPA defaults of 25% (Table 14.4.3).**					
REI = 2 days	1.0	2.025	0.02309	33	No
REI = 13 days	1.0	0.635	0.00724	106	Yes
Irrigation, hand set: <u>Potatoes, pre-emergence.</u> **Assumed scant weed infestation. Assumed fraction of sprayed linuron retained = 10% (Table 14.4.3).**					
REI = 3 days	1.5	1.094	0.01247	62	No
REI = 7 days	1.5	0.717	0.00818	94	No
REI = 8 days	1.5	0.646	0.00736	105	Yes
Irrigation, hand set: <u>Sweet potato cuttings, freshly planted.</u> **Assumed no weed infestation. Assumed fraction of sprayed linuron retained = 5.8% (Table 14.4.3).**					
REI = 0 days	1.0	0.580	0.00661	116	Yes
Notes to table: **AR: Maximum App. Rate** is the *Calculated kg linuron / ha, maximum* in Table 14.4.1. **REI:** Re-entry interval. **TCs:** Transfer coefficients (Annexure 1). Inhalation exposure is not calculated, because inhalation exposure is not calculated (see Sections 7.2 and 14.4).					

14.5 Linagan® SC risk results and discussion

14.5.1 Mixing/spraying/application

All MOEs discussed in this section were calculated with a toxicity value based on health effects that include possible reproductive effects. Therefore, where health effects are discussed in this section, it includes reproductive effects, which are the CMR hazard of concern for Linagan® SC.

The comparison between MOEs and LOCs for occupational handlers mixing and loading Linagan® SC for spraying with a groundboom indicate that the calculated doses to which these operators are exposed are not associated with a risk to health (all MOES exceed the LOC) (Table 14.4.4). Similarly, a risk to health is not indicated for applicators involved in groundboom broadcast spraying (Table 14.4.4).

Operators mixing, loading and spraying Linagan® SC with the use of a backpack (Table 14.4.5) are exposed to levels associated with a risk to health (MOE less than the LOC) when using the higher concentrations indicated for potatoes. However, using the lower concentrations recommended for carrots and sweet potato cuttings is not associated with a risk to health when using a backpack (Table 14.4.4).

14.5.2 Post-application exposure and risks

<u>Carrots</u>
The comparison of MOEs with LOCs in Table 14.4.6 shows that scouting and weeding by hand on day 1 after application of Linagan® SC is not associated with a risk to health, since all MOE values exceed the LOC. It was assumed that re-entry for these two activities was after crop emergence, that is, assuming more foliage and the USEPA default foliar retention of 25% of sprayed linuron. Therefore, re-entry in fields sprayed prior to crop emergence would also not be associated with a risk to health.

Concern is indicated for setting irrigation pipes by hand. Re-entry of pre-emergence treated fields after up to 3 days, and of post-emergence treated fields up to 12 days, is associated with a risk to health (MOEs are less than the LOC).

However, if re-entry for irrigation purposes can be postponed as follows, a risk to health is not indicated:

- Re-entry after 4 days in fields where crops have not yet emerged.
- Re-entry after 13 days if fields were sprayed after emergence. This period is equal to the REI proposed by the USEPA (2018a).

The above irrigation postponement options are likely not acceptable to farmers. The USEPA (2018a) was of the opinion that farmers would need to water fields after a maximum of 3 days. An increase in the REI for irrigation of carrots would put pressure on farmers to use alternative herbicides, of which the costs in South Africa are unknown. Costs are not the only issue for farmers, since linuron provides timing flexibility as a pre- or post- emergence herbicide (discussed in Section 5). The advantage of this flexibility is probably one of the factors driving the market dominance of linuron for broadleaf weed control in carrots. Another driver is the shortened pre-harvest interval of 14 days, which is at least half the interval for other herbicides that can be used in carrots (see Section 5).

The most sensitive field-based variable influencing the exposure of post-application workers is the amount of sprayed foliage.

As stated by the USEPA (2018a): For pre-emergence applications, linuron is applied directly to the soil, "so there is no foliage". This was reiterated in USEPA (2020): "*When linuron is applied as a pre-emergent herbicide, the crop does not yet have foliage at the time of application, and therefore unlikely that a worker or crop advisor entering the treated field would have dermal exposure to linuron*".

If fields remain practically weed-free at the time of herbicide application after crop emergence, and if "very little foliage" is indeed present at the time of spraying, the following is true for the use of Linagan® SC in South Africa:

- It can be assumed that the fraction of a.i. retained on foliage (Equation 14.1.4) is less than the default of 25%.
- Assuming a fraction less than 25% would lower the calculated dislodgeable foliar residue (DFR), the dermal exposure to linuron, and thus the risk to health.

With regard to post-emergence application, it is most important to note the USEPA (2020) conclusions: *"(T)he EPA has determined that post-application exposure and risks assessed for linuron may represent highly conservative estimates, based on the linuron DFR and transfer coefficient (TC) source data*".

The following main points resulted in over-conservative values:

- Linuron DFR data was derived from three field studies on celery grown to 50 to 70% of final plant size, which resulted in a significant over-estimation of the plant foliage present at the time of post-emergence application, and thus of the amount of foliar linuron residue.
- The TC for handset irrigation activities is from a study with a mature potato crop, with full foliage. The TC is thus a likely overestimation when applied to linuron on carrots, because the carrot application timing for linuron is early post-emergence when "*no significant amount of foliage would be present during the application due to the crop phase, dramatically reducing potential worker exposure to linuron*" (USEPA 2020).

In the light of the highly likely over-estimation of dermal exposure to foliar residues and considering the crop production management advantages of Linagan® SC availability to carrot farmers, it is argued that the availability of Linagan® SC as a herbicide option for large-scale carrot farmers should not be discontinued.

This conclusion is in agreement with the USEPA (2020) decision that the recommended PPE for early entry workers (prior to 13 days post-application) performing irrigation activities in treated carrot fields post-emergence should be coveralls over standard clothing, gloves made of water-resistant material, and chemical-resistant footwear, for which waterproof rubber boots would suffice.

Potatoes

Scouting and weeding by hand on day 1 after application of Linagan® SC is not associated with a risk to health, since all MOE values exceed the LOC (Table 14.4.6). These calculations were based on the default of 25% of the fraction of sprayed linuron retained on foliage (Equation 14.1.4).

The Linagan® SC label instructions mandate application to potato fields only prior to crop emergence. Assuming a scant weed infestation at the time of spray application (10% fraction of a.i. retained on foliage), concern is indicated for setting irrigation pipes by hand. Re-entry after up to 7 days, for irrigation purposes, of fields treated pre-emergence, is associated with a risk to health (MOEs are less than the LOC).

However, if re-entry for irrigation purposes can be postponed to 8 days, a risk to health is not indicated (MOE more than the LOC). Potato sprouts might start emerging by day 8, but since these cannot have retained any herbicide (spraying is allowed only prior to emergence), dermal contact with sprouts will not result in a risk to health.

It is unlikely that irrigation postponement would be acceptable to farmers, as it appears that potatoes should be irrigated approximately twice a week after planting, which would indicate re-entry for irrigation by day 3 or 4.

The reasoning for pre-emergence re-entry is the same as for carrots, namely, *"when linuron is applied as a pre-emergent herbicide, the crop does not yet have foliage at the time of application, and therefore unlikely that a worker or crop advisor entering the treated field would have dermal exposure to linuron*" (USEPA 2020).

<u>Sweet potato cuttings</u>
All MOE values calculated for scouting and weeding by hand exceed the LOC if re-entry 1 day after application of Linagan® SC is assumed. This is based on the default fraction (25%) of sprayed linuron retained on foliage (Equation 14.1.4).

The treatment practice recommended on the Linagan® SC label is rather unique. Spraying is recommended immediately after transplanting, before active growth starts, followed by "*light sprinkle irrigation after application to wash herbicide off the leaves of the cuttings*".

Post-application re-entry for the purpose of hand-setting irrigation pipes is thus likely to happen on the day of application (0 days post-application). Calculations showed that this activity, even if the re-entry interval is zero, is not associated with a risk to health, since the calculated MOE exceeds the LOC (Table 14.4.6). These calculations were based on a 5.8 % fraction of sprayed linuron retained on the few leaves remaining on potato cuttings, and assuming that weeds are absent at the time of planting.

Herbicide spraying was assumed to not take place after planting, and MOEs were not calculated for treatment of fields with actively growing plants.

15 Summary of conclusions

- Herbicide use of Linagan® SC is claimed for carrots, potatoes and sweet potato cuttings. Carrots can be sprayed pre- and post-emergence, potatoes only pre-emergence, and sweet potato cuttings are sprayed immediately after planting.

- Backpack operators mixing, loading and spraying solutions with the higher concentrations of Linagan® SC indicated for potatoes are exposed to levels of linuron associated with a risk to health, including reproductive effects. However, using the lower concentrations recommended for carrots and sweet potato cuttings is not associated with a risk to health (or reproductive effects) when using a backpack.

- Operators mixing and loading Linagan® SC solutions for application by groundboom broadcast spraying are exposed to levels of linuron that are not associated with a risk to health (including reproductive effects). This conclusion is valid even if higher concentrations recommended for potatoes are handled, and assuming that all preparations are done according to the label instructions.

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

- Post-application re-entries after 1 day for the purpose of scouting fields and crops, and for weeding by hand, are not associated with a risk to health (or reproductive effects).

- Post-application re-entry of pre-emergence carrot and potato fields for the purpose of hand-setting of irrigation pipes is not of concern with regard to health (or reproductive effects).

- Potential risks to health (including reproductive effects) are of concern for unprotected post-application re-entry of carrots post-emergence, in order to set irrigation pipes by hand. An extended re-entry interval of 13 days is recommended for irrigation purposes, during which workers should wear coveralls over standard clothing, gloves made of water-resistant material, and chemical-resistant footwear, for which waterproof rubber boots would suffice.

- Sweet potato cuttings are sprayed immediately after planting, and are given light sprinkle irrigation after application to wash herbicide off the leaves of the cuttings (Linagan® SC label instructions). Calculated dermal linuron exposure doses during this irrigation practice is not associated with risks to health.

16 Recommendations

An application for the restricted use of the linuron-containing commercial herbicide Linagan® SC should be granted according to the intended product use:

- Herbicide not for sale to and used by residential gardeners.
- Preparation of the treatment solution in accordance with the instructions on the product label.
- Small-scale farmer herbicide application by backpack and hand-held wand on crops should be restricted to carrots and sweet potato cuttings. The activity of sequential mixing, loading and applying with a backpack the required higher herbicide concentration for pre-emergence potatoes is associated with a risk to health. This risk is not applicable to the use of groundboom sprayers.
- Mixing/loading and applying the herbicide with a groundboom is not associated with a risk to health, and also not a risk of reproductive effects, for spraying of carrots (pre- or post-emergence), pre-emergence potatoes of freshly-planted sweet potato cuttings, as described on the product label.
- Personal hygiene instructions on the SDS must be followed; that is, washing hands, forearms and face thoroughly after handling chemical products.
- 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).
- The recommended 1-day post-application restricted-entry interval must lapse before crop re-entry for crop-inspection (scouting) or weeding by hand.
- As indicated on the label, sweet potato cuttings are sprayed immediately after planting, and are given light sprinkle irrigation after application to wash herbicide off the leaves of the cuttings. Exposure to the herbicide during this irrigation practice is not associated with risks to health, because of the scant foliage present at this stage.
- The recommended 1-day post-application restricted-entry interval must lapse before crop re-entry for the purpose of hand-setting of irrigation pipes in sprayed pre-emergence carrot and potato fields.
- In the case of sprayed post-emergence carrots, the restricted-entry interval is 13 days for hand-setting of irrigation pipes. During this period, workers entering the fields for irrigation purposes must wear double-layered clothing, that is, a coverall over basic clothing and water-resistant gloves and shoes (e.g., rubber boots).

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18 Annexure 1

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

Crop group USEPA TC Table	Crop USEPA TC Table	Crop assessed in this report	Activity	Transfer coefficient (TC) cm²/hr
Vegetable, "root"	Carrots	Carrots	Irrigation, hand set	1 900
Vegetable, "root"	Carrots	Carrots	Scouting	210
Vegetable, "root"	Carrots	Carrots	Weeding by hand	70
Vegetable, "root"	Carrots	Carrots	Irrigation (non-hand set) & all mechanised activities	0
Vegetable, "root"	Potatoes	Potatoes	Irrigation, hand set	1 900
Vegetable, "root"	Potatoes	Potatoes	Scouting	210
Vegetable, "root"	Potatoes	Potatoes	Weeding by hand	70
Vegetable, "root"	Potatoes	Potatoes	Irrigation (non-hand set) & all mechanised activities	0
Vegetable, "root"	Potatoes	Sweet potato cuttings	Irrigation, hand set	1 900
Vegetable, "root"	Potatoes	Sweet potato cuttings	Scouting	210
Vegetable, "root"	Potatoes	Sweet potato cuttings	Weeding by hand	70
Vegetable, "root"	Potatoes	Sweet potato cuttings	Transplanting of cuttings from treated plants – not applicable to herbicides such as Linuron	230
Vegetable, "root"	Potatoes	Sweet potato cuttings	Irrigation (non-hand set) & all mechanised activities	0