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Retrieval and scientific interpretation of ecotoxicological information

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INFOTOX Document No 016-2025 Rev 4.0: Response to UnPoison's Comments on the INFOTOX Toxicological Risk Assessment for the Purpose of Derogation of KNERSUS® 200 SL (L10631) (INFOTOX Report No 031-2024 Rev 3.0)

1 Introduction

Scientific documents, and also INFOTOX risk assessment reports, are regularly peer reviewed by other specialists in the relevant fields and it is thus not surprising that the glufosinate ammonium risk assessment reports have been reviewed by third parties. In the case of the INFOTOX reports the expected fields of expertise are Toxicology or Epidemiology.

2 Responses to the report by UnPoison

This INFOTOX report has been compiled in response to:

"Comment on the notices and toxicology risk assessments prepared by Infotox for ALL Glufosinate Ammonium derogation applications", submitted to the Registrar on 14 February 2025, signed by Anna Shevel, Network Coordinator. There is no indication of contributors to the report other than Me Shevel.

The author found the INFOTOX reports *"unacceptably inaccurate and incomplete"*, and threatens the Registrar that *"(S)hould these applications be approved, they will certainly be challenged"*.

UnPoison should consider the fact that the decision of the Registrar regarding Derogation of the CMR constituent is based on the effective management of risk.

The statements by UnPoison conveys a number of inaccuracies and detailed INFOTOX responses are presented below. Comments from UnPoison were copied directly.

UNPOISON COMMENT

1. The derogation applications are based on risk assessments (RA), mainly those done by the USEPA, whereas South Africa's ban is based on hazard assessment and CMR 1A and 1B classification as a 'cut-off' criterion. RAs are based on exposure estimates, utilising mathematical models.

INFOTOX RESPONSE

Sections 3 and 4 of the INFOTOX report deals with hazards and risks.

UNPOISON COMMENT

2. The companies submitted risk assessments for their products containing glufosinate ammonium, however, they did not indicate the CAS numbers for their products so that their formulations could be properly assessed, they only indicated the CAS number for the active ingredient.

INFOTOX RESPONSE

A CAS number (short for Chemical Abstracts Service Registry Number) is a unique numerical identifier assigned to chemical substance described in the open scientific literature. CAS numbers are assigned to pure substances (e.g., single compounds in the herbicide mixture) but are not regularly assigned to mixtures. KNERSUS® 200 SL has not been assigned a CAS number.

UNPOISON COMMENT

3. The executive summaries and the risk assessment reports prepared by Infotox for all the manufacturer's and their brands are exactly the same, word for word, making it impossible for the risk assessments to be correct, as the products do not have exactly the same formulations, and so cannot have the exact same risk assessment outcomes.

INFOTOX RESPONSE

There are indeed certain parts of the health risk assessments for the various products of manufacturers that are the same, because discussions about human and environmental toxicology of glufosinate ammonium would be the same. Differences would be according to label instructions and selected crop applications, that have been considered in the health risk assessment. It is irrational to conclude that it would be impossible for the risk assessments to be correct.

UNPOISON COMMENT

4. According to the 'Guideline for the application for a derogation for an agricultural remedy identified as a substance of concern' published by Department of Agriculture, April 2024, section 2.2.2, derogations will only be granted for a specific period and restricted uses, but these specifications (specific period, restricted use) are missing from the risk assessments supplied.

INFOTOX RESPONSE

It is expected that the period for which derogations are granted are at the discretion of the Registrar. INFOTOX has in fact referred to restrictions in the Executive Summary and in the sections on Recommendation in the text.

3 Responses to UnPoison's "*Key issues identified in the reports*".

UNPOISON COMMENT

1. Inaccurate Interpretation of Margins of Exposure (MOE) and Levels of Concern (LOC): In Section 6, the human health risk assessment methodology compares MOE values to LOC to evaluate risks. However, the report incorrectly states on page 6 (1st paragraph) that a calculated MOE higher than the LOC implies risk is unlikely. This interpretation is incorrect; the correct principle is that if the MOE is lower than the LOC, the risk is unlikely. If this misunderstanding

underpins the calculations, the data suggests a strong potential for adverse health effects.

INFOTOX RESPONSE

The author's statement is incorrect. The MOE is a numerical ratio used in risk assessment to evaluate the potential for harm from exposure to a substance. It compares a reference point (the level of exposure where health effects may occur) to the estimated human exposure level. A higher MOE indicates a greater safety margin between the reference point and actual human exposure. The LOC is the value of the MOE at which the safety margin might not be sufficiently large to exclude concern about harmful exposure. Therefore, concern is warranted if the MOE calculated for human exposure is lower (smaller margin of safety) than the LOC.

UNPOISON COMMENT

2. Omission of Relevant Exposure Routes: The assessment excludes potential exposure from spray drift, stating that no aerial spraying will occur. However, boom spraying, which is part of the application's proposed use, also results in spray drift and subsequent exposure. This omission compromises the thoroughness and reliability of the health risk assessment.

INFOTOX RESPONSE

Spray drift must be controlled, as the herbicide can damage crops. Also, it is stated that spraying should only take place on days without wind. Nonetheless, bystander exposure to spray drift has been addressed in the updated Toxicological Risk Assessment for the Purpose of Derogation of KNERSUS® 200 SL (L10631) (INFOTOX Report No 031-2024 Rev 4.0). There are no health risks, even in a realistic worst-case condition of use, when a toddler is standing only 2 m away from where weeds are being sprayed.

UNPOISON COMMENT

3. Additional substances: The additional substances (co-formulants) that make up the formulations as mentioned on the labels were not mentioned in the risk assessments. This is a requirement to include all the formulants in the risk assessment, not just the active ingredient according to the Registrar's requirements (Section 3(h)(ii)).

INFOTOX RESPONSE

The author confuses the Derogation Application with Application for Registration, as outlined in Government Gazette No 51368 of 11 October 2024. Such registration requires submission of a full dossier that covers all required information. The formulations under consideration have all gone through the registration process, and the current Derogation Applications deals with constituents that have CMR properties.

UNPOISON COMMENT

4. Residential exposures: This is dangerously incorrect. The RA must take into account the potential spray drift of glufosinate ammonium into non-occupational settings, that WILL result in exposures to the farm dweller families, adults and children occupying homes on the farms, and surrounding residential areas. It is well documented that crops are mostly sprayed without warning, often with workers still in the fields, or with immediate re-entry, and no adherence to buffer zones. The potential risks to children, the elderly and vulnerable farm dweller groups and farm town residents, as well as schools must be considered. This is lacking in the risk assessment.

An additional omission in the risk assessments is the section on aerial applications with regards to spraydrift as they indicate it will not be registered for aerial spraying. Boom spraying IS however

registered and this should include the same type of RA as that of aerial spraying.

Boom sprayers also cause spray drift, non-target kills, and neighbouring crop losses etc. The RAs simply state that the premise that it is safe. This doesn't take into account the certain exposure to GA that does and will continue to occur in farm dwellers' homes, and the residential areas surrounding the sprayed crops, impacting the groups mentioned above.

GA is not for domestic use, and use this statement upon which to base the premise that it is safe. This doesn't take into account the certain exposure to GA that does and will continue to occur in farm dwellers' homes, and the residential areas surrounding the sprayed crops, impacting the groups mentioned above.

INFOTOX RESPONSE

The comment is similar to comment 6 on spray drift. INFOTOX's response is as for Comment 6: Spray drift must be controlled, as the herbicide can damage crops. Also, it is stated that spraying should only take place on days without wind. Nonetheless, bystander exposure to spray drift has been addressed in the updated Toxicological Risk Assessment for the Purpose of Derogation of KNERSUS® 200 SL (L10631) (INFOTOX Report No 031-2024 Rev 4.0). There are no health risks, even in a realistic worst-case condition of use, when a toddler is standing only 2 m away from where weeds are being sprayed.

Furthermore, UnPoison states that *"it is well documented" that "crops are mostly sprayed without warning, often with workers still in the fields, or with immediate re-entry, and no adherence to buffer zones" (INFOTOX emphasis)*. These statements identify occasions of failure of sound pesticide management principles, and cannot be used as an argument to discredit the health risk assessments. For many chemicals in use worldwide, safe handling is regulated and supported by product labels and safety data sheets.

The remainder of the section is not based on facts, but on emotional bias. Reference to exposure of children, the elderly and vulnerable farm dweller groups and farm town residents, as well as schools, is not relevant in the applicable agricultural exposure scenarios.

UNPOISON COMMENT

5. Chronic exposure: While all the applicants claim negligible risks based on the USEAP (2013) calculations, there is a 2023 publication by Simoes et al., describing an association between glufosinate ammonium (GA) exposure and lower birth-weight. Another, older paper by Garcia et.al, 1998, states that the data they analysed indicates a 'possible risk of congenital malformations for paternal exposure to GA'.

INFOTOX RESPONSE

The author casts doubt on the USEPA (2013) document, but does not say what the problem is. Reference is made to two publications, but full literature references are not provided, which is not in accordance with scientific writing. INFOTOX found the reference to Simões et al., as:

Simões M, Vermeulen R, Portengen L, Janssen N and Anke Huss A. 2023. Exploring associations between residential exposure to pesticides and birth outcomes using the Dutch birth registry. Environment International, Volume 178, August 2023, 108085.

The final recommendation in this publication is:

"Confirmatory investigations on these and/or similar compounds is warranted". At best, the contents of this publication can be regarded as interesting, but certainly not conclusive. Lower birth weights

are an example of a developmental effect, indicating the known chemical hazard already recognised in the GHS hazard classification.

It was not considered useful to search for the paper by Garcia et.al, 1998, because it refers to a “*possible risk*” of a health effect, which can at best only be used to infer a hazard of developmental effects, which is already recognised in the GHS hazard classification of glufosinate ammonium.

UNPOISON COMMENT

6. Dietary exposure: The direct consumption of commodities on the farms by the farm workers and their families need to be included as they consume the commodities before the commodities are ‘cleaned’ for consumer consumption.

INFOTOX RESPONSE

It is clearly stated in the INFOTOX health risk assessments that “*(D)ietary exposure of consumers of treated produce is highly unlikely and not an issue of concern, firstly because the herbicide is never applied directly to the commodity to be harvested. Secondly, translocation of glufosinate ammonium within the various parts of the plant, e.g., root-to-fruit, is insignificant*”. This will not be different for commodities in the diet of farm workers.

UNPOISON COMMENT

7. Environmental fate and ecotoxicity: The RAs fail to link the environmental fate and ecotoxicity to the ecological RA. Glufosinate ammonium is persistent in the soil for 87 days. This persistence provides a link to the hepatotoxicity and reproductive disruption of male lizards and mouse sperm, and spatial memory impairments, hippocampal MRI modifications and glutamine synthetase activation in mice (Calas et al., 2008), leading to cerebral alterations after chronic exposure to GA.

With regards to laboratory animal studies, Ma et al., 2022 describes epigenetic changes in mice at a dose of 0.2 mg/kg body weight. This dose is much lower than the US EPA reference dose of 6 mg/kg used for the risk assessment calculations. These histone modifications in mouse sperm are not ‘toxicological endpoints’, but indicators of a mode of action for changes in the toxicity endpoints.

The effects on earthworms and non-target arthropods is also significant with acute toxicity, growth, reproductive toxicity, the activity of antioxidant and detoxification enzymes, and DNA damage being shown by Bingjie, Lei, Bo & Yong, 2022.

A study by Castelli et al., 2023, demonstrated how GA altered the number of gut bacteria and/or microbiota composition in honey bees; it showed how GA affected the immunocompetence; and how honey bee lifespan was reduced, indicating an overall negative impact on honey bee health.

INFOTOX RESPONSE

Glufosinate ammonium persistence in soil: The cited 87 days is derived from Section 7.3 of the INFOTOX report. It is the highest soil half-life¹ reported in that section, applicable to *anaerobic soil*, which in practical environmental terms occurs in waterlogged soil². Agriculture in South Africa does not grow crops in water-logged soil. Therefore, choosing this value on which to base an

¹ Soil half-life: the time it takes for 50% of a specific chemical substance to disappear from the soil through degradation processes like biodegradation.

² Waterlogged soil is completely saturated with water, meaning the pore spaces are filled with water instead of air. This occurs when water cannot drain away adequately. Waterlogged conditions can suffocate plant roots, leading to root rot and other issues.

environmental assessment of the risks to lizards and mice would be invalid, because lizards and mice will not live in or on water-logged soil.

UnPoison referred to publications without providing the full literature references, consequently, the papers cannot always be traced. Nonetheless, commentary notes on the listed references are presented, with quotes from articles in *Italic*.

Andre-Guilhem Calas, Olivier Richard, Sandra Meme, Jean-Claude Beloeil, Bich-Thuy Doan, et al.. Chronic exposure to glufosinate-ammonium induces spatial memory impairments, hippocampal MRI modifications and glutamine synthetase activation in mice. *NeuroToxicology*, Elsevier, 2008, 29, pp.740-747.

Mice were treated during 10 weeks three times a week with 2.5, 5 and 10mg/kg of GLA:

The study is not valid for extrapolation to a scenario of environmental exposure of mice, since the route of exposure used in the study – Intraperitoneal injection, the injection of a substance into the peritoneum (body cavity) – is not applicable to exposure of mice in a treated field. Therefore, the results of the study do not mean anything for exposure of mice in treated fields. Furthermore, it is stated in Sections 7.3 and 7.4 of the INFOTOX report that glufosinate ammonium biodegraded moderately rapidly in aerobic soils, with terrestrial field dissipation studies showing soil half-lives of 8-to-17 days in the upper 15 cm of soils. This means that chronic (sustained) high-level exposure in soil, for a period of 10 weeks after application, at the concentrations required to achieve even the lowest internal test dose of 2.5 mg/kg, which was without effect in the Calas study, is practically not possible. In conclusion, the study information is not useful to determine risks in mice, or other mammals.

Ma X, Wang B, Li Z, Ding X, Wen Y, Shan W, Hu W, Wang X, Xia Y. Effects of glufosinate-ammonium on male reproductive health: Focus on epigenome and transcriptome in mouse sperm. *Chemosphere*. 2022 Jan;287(Pt 4):132395. doi: 10.1016/j.chemosphere.2021.132395. Epub 2021 Sep 28. PMID: 34597628.

These results suggested that GLA predominantly impaired sperm epigenome and transcriptome in mice, with little effect on fertility, testis histology or semen quality. Further studies on human sperm using similar strategies need to be conducted for a better understanding of the male reproductive toxicity of GLA.

Ma et al. actually state that the genetic effects caused *little effect on fertility, testis histology or semen quality*. This means that the genetic effects were not sufficient to cause an effect on fertility, and the study is thus not useful to delineate risks to mice. Since “*changes in the toxicity endpoints*” (UnPoison quote), the endpoint being fertility, was not found in the Ma et al. study, there is no evidence that a “*mode of action*” is relevant. Thus, the UnPoison comments do not change the validity of the INFOTOX risk assessment.

A study by Bingjie, Lei, Bo & Yong, 2022 on glufosinate ammonium effects in earthworms was not found in scientific publications, despite a thorough internet search. INFOTOX cannot offer any comments.

Castelli L, Branchiccela B, Zunino P, Antúnez K. Insights into the effects of sublethal doses of pesticides glufosinate-ammonium and sulfoxaflor on honey bee health. *Sci Total Environ*. 2023 Apr 10;868:161331. doi: 10.1016/j.scitotenv.2022.161331. Epub 2023 Jan 7. PMID: 36623662.

The following main findings are relevant to the survival of honey bees: *The chronic exposure to glufosinate ammonium decreased the honey bee's lifespan. Lethal time 50 was estimated at 10 and 11 days for honey bees treated with GA 500 and 50 µg/ml respectively. Acute exposure to glufosinate ammonium also decreased the honey bee's lifespan. Lethal time 50 was estimated at 23 days for the control group and 17 days for honey bees exposed to glufosinate ammonium (500*

µg/ml). Alteration of gut microbiota are shown, indicating decreased immunocompetence, which may lead to an increased susceptibility to pathogens.

The effects shown in this study are not disputed, but the relevance of these effects to the application of KNERSUS® 200 SL is uncertain, due to the following considerations:

It is not clear whether the applied doses are relevant to environmental concentrations in nectar/pollen from treated weeds (crops are not treated), or in honey.

Bees drink water, and the concentrations used in the study are relevant to spray application solutions. However, spray droplets on weeds are unlikely to last for more than a few hours in the South African climate. Therefore, regarding spray droplets, the acute exposure period used in the Castelli et al. study (48 hours) is not relevant, and also not the chronic lifespan exposure – honeybees lifespan is 40 to 60 days, the total treatment period in the Castelli et al. study appears to be approximately 30 days.

Considering nectar/pollen from treated weeds, the following study is relevant:

Li Y, Wang F, Lin Q, Deng P, Zhang Y, Hu D (2022) The Fate and Behavior of Glufosinate-enantiomers and Their Metabolites in Open-Field Soil and Weeds. Arabian Journal of Chemistry 15: 104191:

When glufosinate was given at the peak of weed growth in three orchards, it was mostly distributed and degraded in the weeds, with little remaining in the soil. The two glufosinate enantiomers degraded rapidly in the weeds and soils, with half-lives ranging from 0.7 to 3.1 days. Assuming that the half-life in weeds (0.7 to 2.4 days) is the approximate half-life in pollen, the chronic exposure period used in the Castelli et al. study is certainly too long to be applicable, and the acute exposure period (48 hours) may also be too long.

Considering concentrations of glufosinate ammonium in honey, South African studies are not available, but the highest concentration reported in Canada (where glufosinate ammonium is registered for use) is 33 µg/kg honey. Given a density of 1.5 kg/litre (<https://kg-m3.com/material/honey>), the concentration of glufosinate ammonium in Canadian honey is approximately 50 µg/litre, or 0.050 µg/ml, which is orders of magnitude lower than the lowest concentrations of 50 µg/ml used to treat bees in the Castelli et al. study.

In conclusion, the Castelli et al. study cannot be used to infer a definite high risk to bees, because it is not certain that the periods and concentrations of exposure are relevant to weeds treated with glufosinate ammonium.

UNPOISON COMMENT

8. The main UnPoison comment is that *All the GA products have different co-formulants as indicated in the table* (compiled by UnPoison). *The risk assessments only looks at the CMR risks but not the other potential human health risks.*

INFOTOX RESPONSE

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*”. Therefore, the derogation process cannot be faulted for focussing on the CMR risks.

4 Conclusion

All of the comments by UnPoison that were within INFOTOX's Toxicologist field of expertise, and all

comments on the risk assessment has been answered. Bystander exposure has been additionally included in the updated INFOTOX report *Toxicological Risk Assessment for the Purpose of Derogation of KNER SUS® 200 SL (L10631) Substance of Concern: Glufosinate Ammonium*. Other additional risk assessment work, pursuant to UnPoison's comments, are not indicated, as all comments have been addressed in this response document.

A handwritten signature in black ink, appearing to read 'Willie van Niekerk', is written over a circular professional seal. The seal contains the text 'PROFESSIONAL ENVIRONMENTAL TOXICOLOGIST', 'WILLEM C. VAN NIEKERK', 'QUALIFIED ENVIRONMENTAL PROFESSIONAL', 'No. 07980160', and 'INSTITUTE OF PRACTICE' around a central star.

Willie van Niekerk PhD; Environmental Toxicologist QEP(USA); Pr Sci Nat (Environmental Science).
Managing Director

A handwritten signature in black ink, appearing to read 'Marlene Fourie', is written in a cursive style.

Internal review: Dr Marlene Fourie PhD (Reproductive Biology); MSc (Epidemiology);
Pr Sci Nat (Toxicological Science).