UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: November 8, 2022

SUBJECT: **Chlorophacinone, Diphacinone and its Sodium Salt, Brodifacoum, Bromadiolone, Difenacoum, Difethialone.** Response to Comments for the Draft Human Health Risk Assessment for Registration Review.

PC Codes: 067707, 067701, 067705, 112701, 112001, 119901, 128967
Decision No.: 565264
Petition No.: NA
Risk Assessment Type: Response to Comments
TXR No.: NA

MRID No.: NA

DP Barcode: D458953

Registration No.: Multiple
Regulatory Action: Registration Review
Case Nos.: 2100, 2205, 2755, 2760, 7630, 7603
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40 CFR: NA

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Pesticide Re-evaluation Division (PRD; 7508M)

The Pesticide Re-evaluation Division (PRD) has received comments on the human health draft risk assessment (DRA) for the first-generation anticoagulant rodenticides (chlorophacinone, diphacinone and its sodium salt) and second-generation anticoagulant rodenticides (brodifacoum, bromadiolone, difenacoum, and difethialone) active ingredients in support of Registration Review (05/04/2020; *Registration Review: Draft Human Health and/or Ecological Risk Assessments for Several Rodenticides*; Docket ID: EPA-HQ-OPP-2015-0768-0040). Summaries

of the comments pertaining to the first- or second-generation anticoagulant rodenticide active ingredients are provided below, along with the Health Effects Division (HED) responses.

HED Response to Comments from the Director, United States Department of Agriculture – Office of Pest Management Policy (USDA-OPMP)

USDA-OPMP Comment: "USDA generally supports EPA's reasonable streamlined approach to the preliminary draft human health and ecological risk assessments…USDA stands ready to provide EPA with additional information on the benefits of these rodenticides, as well as additional characterization information to help address and/or refine EPA's risk estimates, if needed."

HED Response: EPA appreciates additional information provided by the USDA when requested regarding the importance of continued registration of various rodenticide products, their benefits, and additional characterization especially as they relate to conservation, agriculture, and public health uses.

USDA-OPMP Comment: "USDA compliments EPA on the efficient, qualitative approach employed in the draft human health risk assessments for six anticoagulant rodenticides (chlorophacinone, diphacinone, brodifacoum, bromadiolone, difenacoum, and difethialone). The hazard profiles for these rodenticides are well established, and USDA supports EPA's decision to waive a number of required toxicity studies. We note that EPA requires no additional toxicity or exposure data at this time, as such data would not significantly advance EPA's understanding of the hazards posed by these substances, nor would it alter the risk management goal of reducing exposure to the extent possible to limit any potential risk."

HED Response: EPA appreciates the USDA's readiness to provide additional characterization for these six anticoagulant rodenticides should such data significantly advance the EPA's understanding of the hazards posed.

USDA-OPMP Comment: "USDA appreciates EPA's updated analysis of available incident data, which suggests that EPA's 2008 Risk Mitigation Decision (RMD) for Ten Rodenticides contributed to an overall decline in human incidents involving rodenticide products, particularly for residential cases involving SGARs (USEPA, 2008). We note that the RMD sought specifically to minimize children's exposure to rodenticide products used in homes by prohibiting loose bait formulations (*i.e.*, pellets and meal); requiring that bait products marketed to general and residential consumers be sold only with bait stations; and prohibiting the use of SGARs in residential consumer products."

"Through the RMD, EPA also implemented a number of bait placement restrictions; packaging size requirements; and distribution provisions for structural professional and agricultural use products. In implementing these measures, EPA was able to reduce exposure while avoiding substantial costs that would have been incurred had the SGARs been reclassified as restricted use pesticides. USDA believes that the appropriateness of these actions, from a human health standpoint, are reflected in the very low frequency and largely minor severity of occupational incidents reported between 2011-2019."

HED Response: EPA appreciates the support for mitigation presented in the RMD. EPA will continue to monitor incident data moving forward.

HED Response to Comments from Neogen Corporation

Neogen Comment: It is unclear how the conclusion from the Risk Assessment was made that labels should be modified to assure that occupational exposures are limited. Nothing within the Risk Assessment clearly leads to this conclusion. If the data for occupational exposures is supposed to lead to this conclusion, we would point out that in the majority of occupational exposure cases from the March 4, 2020 Tier I Update Review of Human Incidents, the rodenticide of primary concern is zinc phosphide which is not an anticoagulant rodenticide or covered by this Risk Assessment. Additionally, the Tier I Update Review of Human Incidents states, "Overall, there was a low frequency of occupational incidents reported in SENSOR-Pesticides, California PISP, and Main IDS."

HED Response: The 2020 DRA states, "Based upon the available hazard and toxicity profile, HED concludes that FGAR and SGAR pesticides are extremely acutely toxic by all routes of exposure. Labeled uses of these products should be modified, as needed, to assure that occupational dermal and inhalation exposures are limited to the extent possible." Many labels already indicate gloves among the listed personal protective equipment, while respiratory protection is not indicated. Thus, the recommendations for labels to include respirators and consistently include protective gloves, serves to limit potential occupational exposures. Moreover, incident data reflects health effects due to acute exposures (*e.g.*, spills, releases, or other unintentional exposures). Association between potential adverse effects related to chronic, or repeat exposures over time, are not addressed in incident data. Incident reports are not a surrogate to, nor refinement measure, for risk assessments but instead represent a useful adjunct to them. Incident data can provide important product end-user exposure information, but the data alone do not represent the risks posed by a compound. HED will continue to monitor incident trends for all registered rodenticide active ingredients to see if trends of concern are identified.

Neogen Comment: [W]e fail to see a clear path for mention of respiratory protection in PPE for occupational handlers. We would like to call your attention to MRID 44888101 which is an occupational exposure evaluation for personnel exposed to anticoagulants during manufacturing processes. While this study looks at the chronic exposure of employees to anticoagulants, it should be pointed out that, despite regular exposure to these actives without respirators, there were no acute exposure issues. If needed, we can provide additional years of data to demonstrate that the trend continues.

Further to the point on respiratory protection, most "loose" formulations of the anticoagulant rodenticides are manufactured in such a way as to reduce the risk of the product generating a dust. This is accomplished in ways such as the addition of oils or in the use of extrusion in pellet formation. We would strongly suggest that the agency take a formulation based approached if considering a requirement for respiratory protection rather than using a broad strokes approach.

HED Response: The submission, MRID 44888101, was reviewed for potential human studies review board (HSRB) issues and found that the activities of the individuals in the subject

submission do not constitute human subject research nor do the requirements for the Human Studies rules apply. HED has also reviewed the submission and determined that there are several deficiencies that preclude its use in informing HED further, including: 1) details about the control population (*e.g.*, number of individuals tested, age, gender, socioeconomic status), 2) details regarding population tested (*e.g.*, age, gender, socioeconomic status), 3) information regarding methods of testing prothrombin (what assay methods were used), 4) no formal statistics were conducted, 5) discussion regarding variance in values and for values lower than the reference prothrombin time, 6) lack of any quantitative exposures in the study, 7) lack of any details regarding personal protective equipment or environmental controls used in the manufacturing, and 8) lack of any formulation-specific data in the study. Furthermore, the Agency has concluded that the toxicity profiles of both the SGARs and FGARs are well understood, their toxicity profiles demonstrate adverse effects at low doses (*i.e.*, ug/kg) in repeated dose studies, in multiple species, and via dermal, oral, and inhalation exposure routes, and are classified as Acute Toxicity Category I. HED matches market formulations with the best available exposure data to obtain appropriate surrogates. HED anticipates potential occupational exposures from contact with formulations like granules, tracking powders, and grain meals, as well as waxy/paraffinized or non-paraffinized pellets.

HED Response to Comments from the Responsible Industry for a Sound Environment (RISE)

RISE Comment: Overall, we agree with the draft assessment for the FGARs and SGARs regarding the decrease in exposure incidents and the impacts of the 2008 Risk Mitigation Decision (RMD). Registrants supplying these products continue to support best management practices by professionals applying products to ensure safe and effective use.

HED Response**:** EPA appreciates the support for both the FGAR and SGAR characterization of exposure incidents and the 2008 RMD. EPA also thanks the RISE for supporting the registrants in their handler practices.

RISE Comment: Given the importance of anticoagulant rodenticides to protecting public health and safety we ask the Agency to provide more transparency about its current assessment of occupational exposure from loose/pelleted formulations, which is not consistent with available data or prior agency determinations that such formulations do not pose a higher risk of inhalation and dermal exposure than other formulation types.

HED Response**:** We appreciate the comment from RISE concerning loose/pelleted formulations, HED is concerned with potential occupational exposures from contact with rodenticides. Based on available surrogate exposure and hazard information, HED believes there is potential inhalation exposure from loose formulations such as pelleted baits. Prior to the 2008 RMD, HED noted its concern regarding potential exposure to occupational handlers in the 1999 rodenticide cluster reregistration eligibility decision (RED).

RISE Comment: "...ask that EPA provide greater clarity about its use of incident data to further refine the risk assessment. The data show an overall reduction in exposure incidents, which may be even lower for FGARs and SGARs, given the mix of unusual incidents cited and the inclusion

of non-anticoagulant rodenticides that are not the subject of this registration review. Taken together with the RMD these factors do not support an assumption that the exposure potential for loose formulations has changed. Further, we urge the agency to review and reconsider the applicability of data from the SENSOR and PISP data sets where zinc phosphide exposures are included. This rodenticide is not in the class of chemistry considered by this risk assessment. We note the symptoms detailed from SENSOR and PISP data are those of zinc phosphide exposure, which are not similar to those of anticoagulant rodenticide exposure. Though the data supports findings of a significant decrease in occupational exposures and that a majority of those exposures are generally of low severity, we ask the Agency to reassess which of the 21 incidents have direct application to this risk assessment and use of anticoagulant rodenticides. The anticoagulant rodenticides are important tools in integrated pest management programs, providing significant benefits, as well as options for managing warfarin resistant rodent species with the SGARs.

HED Response: As a standard practice of support for registration review, HED provides a summary of available incident data for reported real-world exposure illnesses from product end-users. Incident data reflects health effects due to acute exposures (*e.g.*, spills, releases, or other unintentional exposures). Association between potential adverse effects related to chronic, or repeat exposures over time, are not addressed in incident data. Incident reports are not a surrogate to, nor refinement measure, for risk assessments but instead represent a useful adjunct to them. Incident data can provide important product end-user exposure information, but the data alone do not represent the risks posed by a compound. HED will continue to monitor incident trends for all registered rodenticide active ingredients to see if trends of concern are identified.

HED Response to Comments from Liphatech, Inc.

Liphatech Comment: "We agree with the Agency's approach of continuing to use the studies it has previously evaluated and based decisions on." ... "We also agree that the human incident data from the multiple databases the Agency reviewed provides a sound basis for monitoring exposure trends."

HED Response: EPA thanks Liphatech, Inc. for their comment. EPA also appreciates the support provided for the anticoagulant rodenticide incidents databases and will continue to monitor incident data moving forward.

Liphatech Comment: "It is not apparent from these two sources of information [previously-evaluated studies and human incident data] why the Agency concludes that occupational dermal and inhalation exposures for 'loose formulations' are anticipated. Statements within the document contradict this conclusion, which also would reverse prior Agency decisions regarding the classifications for inhalation and dermal toxicity. The draft RA also does not explain the statement that labeled uses should be modified to limit exposure. No evidence is given that applications conducted according to the current label uses are resulting in exposures with confirmed symptoms of anticoagulant toxicity. The incident data summarized in the draft RA and the more detailed descriptions in the Tier I Update Review of Human Incidents do not include any examples for which this has occurred.

Although the concerns appear to be based on a review of laboratory toxicity studies demonstrating high toxicity, these studies have been on file with the Agency for decades and were used to determine the toxicity classifications for the product labels. The inhalation toxicity classification of Category III for these formulations is supported by attrition studies that the Agency concluded in a 2001 decision demonstrated that these formulations do not generate significant amounts of inhalable particles during normal use. The draft RA does not indicate that these studies are no longer acceptable to the Agency. Nor is it explained why loose formulations would have a higher risk of dermal exposure than other formulations, or why the previous Agency evaluation was incorrect and the current label requirement of waterproof gloves is no longer considered protective.

The draft RA's review of incident databases concludes that there is a low frequency of occupational incidents and that most were low in severity. Moreover, none of the incidents included the combination of factors that would link an occupational application of a loose formulation of an anticoagulant rodenticide conducted in compliance with the label to symptoms consistent with exposure. Incidents either did not involve an anticoagulant rodenticide (most are for zinc phosphide), did not involve a loose formulation, did not occur during application, resulted from label directions not being followed, or did not report symptoms that the Agency defines as diagnostic of anticoagulant poisoning."

HED Response: The Agency has identified several technical aspects of these attrition studies which preclude their consideration for use in the risk assessment process. The *Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides and Pesticide Products (Acute Oral, Acute Dermal, Acute Inhalation, Primary Eye, Primary Dermal, and Dermal Sensitization)*, considers inhalable particles to be < 100 µm in diameter, but also states that for solid particles > 100 µm, the pesticide does not need to be respirable to pose a hazard, since many chemicals are well absorbed in the nasal mucosa. Given the adverse effects of rodenticides at very low doses, a small percentage of inhalable or respirable particles may pose a potential risk. The study design neither adequately represents anticipated occupational exposure scenarios, nor is sufficient in quantifying respirable particles (< 100 µm). Moreover, the attrition data[1] describe only two "loose" formulations each of bromadiolone and chlorophacinone and cannot be assumed to be applicable to all bromadiolone, all chlorophacinone, all "loose" formulations, or across the currently registered SGARs and/or FGARs. HED concludes that these and additional available attrition studies[2] do not inform nor impact the risk conclusions outlined in the 2020 human health DRA in support of registration review[3], nor HED's reasoned conclusion that potential non-target (*e.g.*, human) exposures should be limited to the extent possible.

Based on the available hazard and toxicity profile, HED concludes that FGAR and SGAR pesticides are highly toxic by all routes of exposure, including both dermal and inhalation exposure. HED believes there is potential inhalation exposure from contact with formulations

[1] MRIDs 45273201, 45273202, 45273203, 45273204.

[2] Additional attrition study MRIDs (46404001, 46395301, and 45815501) for brodifacoum, diphacinone, and zinc phosphide, respectively, were also referenced by a registrant after the public period.

[3] L. Bacon, *et al.,* "*Chlorophacinone, Diphacinone and its Sodium Salt, Brodifacoum, Bromadiolone, Difenacoum, Difethialone; Draft Human Health Risk Assessment for Registration Review of Anticoagulant Rodenticides"*, D456332, 03/20/2020

like granules, tracking powders, and grain meals, as well as waxy/paraffinized or non-paraffinized pellets. In concurrence with the 2001 decision, the data do demonstrate high attrition resistance for most of the products specifically tested (< 1%). However, the data do not demonstrate the absence of attrition of the tested products and do not make a clear distinction in attrition for paraffinized products compared to non-paraffinized products. Thus, while the data were used in 2001 to support acute inhalation toxicity classifications, they are not directly applicable to risk assessment and do not support the claim that these formulations produce negligible inhalation exposure to occupational applicators and other handlers of rodenticide end-use products. Regarding the incident data, incident data reflects health effects due to acute exposures (*e.g.*, spills, releases, or other unintentional exposures). Association between potential adverse effects related to chronic, or repeat exposures over time, are not addressed in incident data. Incident reports are not a surrogate to, nor refinement measure, for risk assessments but instead represent a useful adjunct to them. Incident data can provide important product end-user exposure information, but the data alone do not represent the risks posed by a compound.