Registration Decision RD2024-01

Diflufenican, SC500, SC600, and SC617

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Under the authority of the *Pest Control Products Act,* pesticides must be assessed before they are sold or used in Canada in order to determine that they do not pose unacceptable risks to humans or the environment and have value when used according to the label instructions. The pre-market assessment considers available data and information[1] from pesticide registrants, published scientific reports, other governments, and international regulatory agencies, as well as written comments if received during public consultations. Health Canada applies internationally accepted current risk assessment methods as well as risk management approaches and policies. More details, on the legislative requirements, risk assessment and risk management approach, are provided under the Evaluation Approach section of this document.

Registration decision statement[2] for Diflufenican, SC500, SC600, and SC617

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act,* is granting registration for the sale and use of Diflufenican Technical and SC500 containing the technical grade active ingredient diflufenican, for pre-plant and pre-emergent weed control in corn and soybean; SC600, containing the technical grade active ingredients diflufenican and metribuzin for pre-plant and pre-emergent weed control in soybean; and SC617 containing the technical grade active ingredients diflufenican and isoxaflutole for pre-plant and pre-emergent weed control in field corn.

The Proposed Registration Decision PRD2023-07, *Diflufenican, SC500, SC600, and SC617,* containing the detailed evaluation of the information submitted in support of this registration, underwent a 45 day consultation period ending on 17 September 2023. The evaluation found that, under the approved conditions of use, the health and environmental risks and the value of the pest control product(s) are acceptable. Health Canada received written comments relating to the health risk assessment during the public consultation period conducted in accordance with section 28 of the *Pest Control Products Act*. The written comments were from a private citizen and the registrant.

Comments and responses

Comment on the use of natural alternatives and elimination of animal testing

One commenter advocated for the use of natural alternatives to chemical herbicides, and for the elimination of animal testing.

Health Canada response

Health Canada requires information on the potential toxic effects of pesticides to determine the potential hazards and risks to human health and the environment from pesticide exposure. Toxicity information typically includes, in part, animal testing data generated by pesticide manufacturers.

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1 Information Note – Determining Study Acceptability for use in Pesticide Risk Assessments

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act.*

These studies are conducted according to international testing protocols, which include requirements to ensure protection of the welfare of laboratory animals. This process is used for approving all pesticides in Canada, including non-conventional pesticides (for example, baking soda, citric acid) and microbial pesticides (for example, *Bacillus thuringiensis*).

While animal toxicity testing currently plays a critical role in assessing human health and environmental risks from exposure to pesticides, Health Canada supports the reduction of unnecessary animal testing where scientifically justified. To this end, Health Canada does consider requests from pesticide manufacturers to waive requirements for specific animal studies or to consider validated non-animal alternatives in hazard assessment when feasible and supported scientifically. Health Canada issued guidance for industry on the waiving of mammalian acute toxicity studies in 2013.

Health Canada is also an active participant in various international activities aimed at reducing animal testing while ensuring the protection of human health and the environment. Continued analysis of international trends and approaches is important to ensure continued alignment and harmonization. While non-animal alternatives exist for certain types of tests (for example, in vitro tests for irritation), animal testing continues to provide a more accurate assessment of a variety of other potential effects, and more importantly, information regarding the dose level at which effects may occur, so that this information can then be used to protect human health and the environment.

With respect to the commenter's preference for the use of non-conventional products, it is important that producers have access to a variety of tools that are appropriate for their needs and which can facilitate an integrated pest management strategy that includes consideration of efficacy, resistance management and reduction of pesticide use. Both conventional and non-conventional products that are shown to have acceptable risks are eligible for registration in order to meet these needs.

Comment about the no observed adverse effect level (NOAEL) and the lowest observed adverse effect levels (LOAELs) endpoints

The registrant attests that the changes in methaemoglobin (MetHb) formation at the low dose levels in the 14-day and 28-day dietary toxicity studies in the rat conducted with the soybean seed metabolite, BCS-BT38895, should be considered non-adverse. They indicate that the 14-day study no observed adverse effect level (NOAEL) should be 17.0 and 16.3 mg/kg bw/day for males and females, respectively, while the 28-day study NOAEL should be 4.68 and 3.97 mg/kg bw/day for males and females, respectively. To support their rationale, the registrant states that levels of MetHb in the blood are considered tolerable and safe in humans up to 5% and that the levels less than 1% seen in the low-dose groups in both studies should not be considered adverse. The registrant further notes that changes in MetHb formation occurred in the absence of organ weight changes in the spleen, effects on erythrocyte count hemoglobin concentration, or evidence of Heinz body formation.

Health Canada response

In determining the adversity of the increased MetHb in the blood in the 14-day and 28-day rat toxicity studies with BCS-BT38895, Health Canada considered the statistical significance of the changes, the magnitude of the methaemoglobin values and changes compared to the controls, the low variability within the control groups, and associated changes in the hematopoietic system. Health Canada also consulted the Joint Meeting on Pesticide Residues (JMPR) guidance on setting acute reference doses for pesticides (Solecki et al., 2005)[3] which states that "For acute exposure to methaemoglobin-inducing xenobiotics, ...a statistically significant increase by comparison with controls in rodents is considered to represent a conservative approach to setting an ARfD." A conservative approach when referencing rodent studies was considered justified due to the differences in reducing capacity (MetHb reductase activity) between rodents and humans. Species with higher reducing capacity, such as the rat, also have lower background levels of MetHb; however, a statistically significant increase in MetHb indicates that the residual reducing capacity has been overwhelmed. Therefore, as rats have a higher reducing capacity than humans (Smith, 1996)[4], a change that results in a MetHb level of <1% in rats is likely to be of greater magnitude in humans and potentially outside the tolerable level.

The rationale provided by the registrant is insufficient to address the known physiological differences in sensitivity between rats and humans. Increases in MetHb were statistically significant at all dose levels and the intragroup variability was very low, without a notable overlap between results in different dose groups, with increased spleen weights and extramedullary haematopoeisis observed in males at the lowest dose tested in the 28-day study. Thus, there was a sufficient weight of evidence to conclude that diflufenican metabolite, BCS-BT38895 caused methaemoglobinaemia in rats at the lowest doses tested. In the absence of clear and convincing scientific evidence to support the rationale provided, Health Canada maintains that the lowest observed adverse effect levels (LOAELs) in the 14-and 28-day studies remain at the lowest dose tested in each study, and that NOAELs could not be identified.

Comment regarding the soybean seed aniline metabolite, BCS-BT38895

The registrant expressed concern that Health Canada considered the soybean seed aniline metabolite, BCS-BT38895, to be potentially carcinogenic in male rats. The registrant stated that, in studies on the aniline used by Health Canada as a surrogate (p-chloroaniline) for the soybean aniline metabolite, tumours occurred only in males and only in rats while they did not occur in the mouse. Further, the tumours in the p-chloroaniline studies occurred at doses at which non-neoplastic changes were also observed and these changes were not observed in the 14-day and 28-day studies on the BCS-BT38895 metabolite. The registrant also expressed concern about physiological differences in MetHb reductase activity between species, noting that the highest

[3] Solecki, R, Davies, L., Dellarco, V., Dewhurst, I., van Raaij, M., Tritscher, A. (2005) Guidance on setting of acute reference dose (ARfD) for pesticides, Food and Chemical Toxicology,Volume 43, Issue 11, 2005, Pages 1569-1593, ISSN 0278-6915, https://doi.org/10.1016/j.fct.2005.04.005. (https://www.sciencedirect.com/science/article/pii/S0278691505001419), last accessed 03-Nov-2023.

[4] Smith, RP. (1996) Toxic responses of the blood. In: Klaassen, CD; ed. Casarett and Doull's toxicology: the basic science of poisons. 5th edition. New York, NY: McGraw-Hill; pp. 335–354.

activity is found in mice and hamsters, followed by rats and humans and the lowest activity is found in dogs. The registrant asserted that these species differences may account for the tumour formation in the rat and not the mouse.

Health Canada response

As the toxicity of metabolite BCS-BT38895 was only assessed in short-term (14-day and 28-day) dietary toxicity studies in one species, where pre-neoplastic changes would not be expected, there is insufficient information in the database to determine the carcinogenic potential of BCS-BT38895. Instead, it was determined that the most appropriate estimation of carcinogenicity would be through the use of an analogous compound, p-chloroaniline, which was chosen for its structural similarity to the BCS-BT38895 metabolite.

The comments provided by the registrant are insufficient to address the outstanding concerns regarding the potential carcinogenicity of the soybean seed aniline metabolite. In the absence of clear and convincing scientific evidence to support the comment provided, Health Canada maintains that using p-chloroaniline as an analogous compound to the BCS-BT38895 metabolite is scientifically justified and is considered a health-protective approach.

Comment on the inclusion of increased spleen weights in males at the low dose

The registrant objected to the inclusion of increased spleen weights in males at the low dose in the 28-day dietary rat toxicity study with the metabolite BCS-BT38895 in Table 5 of the proposed registration decision document. The registrant considers the increased weight to be of low magnitude and noted that the change was not statistically significant when compared to controls and that any associated macro- or histopathological changes were slight or non-existent. The registrant considers the changes to be adaptive and attests that the findings should be removed from the table in the final registration decision document.

Health Canada response

In considering the changes at the low dose level in the 28-day rat dietary study with BCS-BT38895, Health Canada included the increased spleen weights in the low-dose males as a treatment-related finding, based on the 10% increase in relative spleen weights and taking into consideration other treatment-related findings, which include increased reticulocytes and MetHb values and increased extramedullary haematopoiesis in males and increased MetHb and reticulocyte values in females. While the registrant considers these changes to be adaptive and not adverse, as stated in the response to the comments pertaining to the increased MetHb above, due to the greater MetHb reductase activity in rats than humans, a conservative approach is considered justified in determining the safety to humans.

Comment on the NOAEL in the 90-day dietary mouse toxicity study conducted with diflufenican

The registrant commented that the NOAEL in the 90-day dietary mouse toxicity study conducted with diflufenican should be the lowest dose tested. Health Canada established the LOAEL in the male mice at the lowest dose tested based on decreased body weight and body weight gain in all

male treatment groups. At the lowest dose tested, body weights and body weight gains in male mice were decreased 10% and 11%, respectively, when compared to the concurrent control group. The registrant considers the decreased body weight at the lowest dose to be adaptive and, as there were no other treatment-related findings at this dose level, the NOAEL should be the lowest dose tested.

Health Canada response

Health Canada considers a decrease in body weight of 5% compared to controls to be an adverse effect in toxicity studies[5,6]. As such, the establishment of the LOAEL in males in the 90-day mouse toxicity study at the lowest dose level was considered to be appropriate.

Comment on the inclusion of decreased thymus weights as treatment-related effects

The registrant objected to the inclusion of decreased thymus weights as treatment-related effects in the 28-day dietary range-finding toxicity study in rats conducted with diflufenican in Table 5 of the proposed registration decision document. The registrant states that the study report "indicates that decreases in thymus weight (absolute and relative) were observed in the mid-dose for females only, while at the high dose, absolute thymus weights were decreased for females only."

Health Canada response

The 28-day dietary toxicity study in rats was a range-finding, supplementary study. This study was considered supplementary due to low animal numbers and limited investigation including a lack of histopathological examination of the tissues. As such, slight changes in organ weights were considered treatment-related as there was no histopathological examination of the thymus that would confirm a lack of adversity of this change. This finding in the range-finding study did not affect the setting of the toxicology reference values for diflufenican.

Other information

The relevant confidential test data on which the decision is based (as referenced in PRD2023-07, *Diflufenican, SC500, SC600, and SC617* are available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

5 Foran, J.A. (1997) Principles for the selection of doses in chronic rodent bioassays. ILSI Risk Science Working Group on Dose Selection. Environ Health Perspect. 1997 Jan; 105(1): 18–20. doi: 10.1289/ehp.105-1469843 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1469843/?page=2), last accessed 12-Dec-2023.

6 OECD (2012). Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Test Guidelines 451, 452 and 453; 2nd Edition. Paris : Organisation for Economic Co-Operation and Development. (https://www.oecd-ilibrary.org/docserver/9789264221475-en.pdf?expires=1702387812&id=id&accname=oid024861&checksum=9F36529D9EDD16810627AF450182D930), last accessed 12-Dec-2023.

Any person may file a notice of objection[7] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides section of Canada.ca (Request a Reconsideration of Decision) or contact the Pest Management Information Service.

[7] As per subsection 35(1) of the *Pest Control Products Act.*

Evaluation approach

Legislative framework

The Minister of Health's primary objective under the *Pest Control Products Act* subsection 4(1) is to prevent unacceptable risks to individuals and the environment from the use of pest control products.

As noted in the preamble of the Act, it is in the national interest that the attainment of the objectives of the federal regulatory system continue to be pursued through a scientifically-based national registration system that addresses risks to human health, the environment and value both before and after registration and applies to the regulation of pest control products throughout Canada; and that pest control products with acceptable risk and value be registered for use only if it is shown that their use would be efficacious and if conditions of registration can be established to prevent unacceptable risk impact to human health and the environment.

For the purposes of the Act, the health or environmental risks of a pest control product are acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product, taking into account its conditions of registration as per subsection 2(2) of the *Pest Control Products Act*.

Risk for the human health and environment, and value are defined under the Act subsection 2(1) as follows:

> **Health risk**, in respect of a pest control product, means the possibility of harm to human health resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Environmental risk**, in respect of a pest control product, means the possibility of harm to the environment, including its biological diversity, resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Value**, in respect of a pest control product, means the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact.

When evaluating the health and environmental risks of a pesticide and determining whether those risks are acceptable, subsection 19(2) of the *Pest Control Products Act* requires Health Canada to apply a scientifically-based approach. The science-based approach to assessing pesticides considers both the toxicity and the level of exposure of a pesticide in order to fully characterize risk.

Pre-market assessments are based on a required set of scientific data that must be provided by the applicants for pesticide registrations. Additional information from published scientific reports, other government departments and international regulatory agencies are also considered.[8]

Risk and value assessment framework

Health Canada uses a comprehensive body of modern scientific methods and evidence to determine the nature as well as the magnitude of potential risks posed by pesticides. This approach allows for the protection of human health and the environment through the application of appropriate and effective risk management strategies, consistent with the purpose described in the preambular text set out above.

Health Canada's approach to risk and value assessment is outlined in A Framework for Risk Assessment and Risk Management of Pest Control Products.[9] A high-level overview is provided below.

i) Assessing potential health risks

With respect to the evaluation and management of potential health risks, Health Canada's risk assessments follow a structured, predictable process that is consistent with international approaches and the Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks.[10]

The evaluation of potential health risks begins with a consideration of the toxicological profile of a pesticide to establish reference doses at which no adverse effect is expected and against which the expected exposure is assessed. This includes, where appropriate, the use of uncertainty (protection) factors to provide additional protection that accounts for the variation in sensitivity among members of human population and the uncertainty in extrapolating animal test data to humans. Under certain conditions, the *Pest Control Products Act* requires the use of another factor to provide additional protection to pregnant women, infants, and children. Other uncertainty factors, such as a database deficiency factor, are considered in specific cases. More details related to the application of the uncertainty factors are provided in SPN2008-01.[11]

Assessments estimate potential health risks to defined populations[12] under specific exposure conditions. They are conducted in the context of the proposed or registered conditions of use, such as the use of a pesticide on a particular field crop using specified application rates, methods and equipment. Potential exposure scenarios consider exposures during and after application of

8 Information Note – *Determining Study Acceptability for use in Pesticide Risk Assessments*

9 PMRA Guidance Document, *A Framework for Risk Assessment and Risk Management of Pest Control Products*

10 Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks - August 1, 2000

11 Science Policy Note: *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*

12 Consideration of Sex and Gender in Pesticide Risk Assessment

the pesticide in occupational or residential settings, food and drinking water exposure, or exposure when interacting with treated pets. Also considered are the anticipated durations (short-, intermediate- or long-term) and routes of exposure (oral, inhalation, or skin contact). In addition, an assessment of health risks must consider available information on aggregate exposure and cumulative effects.

ii) Assessing risks to the environment

With respect to the evaluation of environmental risks, Health Canada's environmental risk assessments follow a structured, tiered approach to determine the likelihood that exposure to a pesticide can cause adverse effects on individual organisms, populations, or ecological systems. This involves screening assessments starting with simple methods, conservative exposure scenarios and sensitive toxicity effects metrics, then moving on, where required, to more refined assessments that can include exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods.

The environmental assessment considers both the exposure (environmental fate, chemistry, and behaviour, along with the application rates and methods) and hazard (toxic effects on organisms) of a pesticide. The exposure assessment examines the movement of the pesticide in soil, water, sediments and air, as well as the potential for uptake by plants or animals and transfer through the food web. The possibility for the pesticide to move into sensitive environmental compartments such as groundwater or lakes and rivers, as well as the potential for atmospheric transport, is also examined. The hazard assessment examines effects on a large number of internationally recognized indicator species of plants and animals (terrestrial organisms include invertebrates such as bees, beneficial arthropods, and earthworms, birds, mammals, plants; aquatic organisms include invertebrates, amphibians, fish, plants and algae), and includes considering effects on biodiversity and the food chain. Acute and chronic effects endpoints are derived from laboratory and field studies that characterize the toxic response and the dose–effect relationship of the pesticide.

The characterization of environmental risk requires the integration of information on environmental exposure and effects to identify which, if any, organisms or environmental compartments may be at risk, as well as any uncertainties in characterizing the risk.

iii) Value assessment

Value assessments consist of two components: an assessment of the performance of a pest control product and its benefits.

Assessing pesticide performance involves an evaluation of the pesticide’s efficacy in controlling the target pest and the potential for the pesticide to damage host crops or use sites. Where the efficacy of a pesticide is acceptable, the assessment serves to establish appropriate label claims and directions and an application rate (or rate range) that is effective without being excessive, and with no unacceptable damage to the use site or host organism/crop (and subsequent hosts or crops) under normal use conditions.

In many cases, proof of performance alone is sufficient to establish the value of the pesticide, so that an in-depth or extensive evaluation of benefits may not be required. However, a more thorough assessment of benefits may be undertaken in particular cases where performance alone does not sufficiently demonstrate value, or while developing risk management options.

Risk management

The outcomes of the assessments of risks to human health and the environment, and the assessment of value, form the basis for identifying risk management strategies. These include appropriate risk mitigation measures and are a key part of decision-making on whether health and environmental risks are acceptable. The development of risk management strategies take place within the context of the pesticide's conditions of registration. Conditions can relate to, among other things, the specific use (for example, application rates, timing and frequency of application, and method of application), personal protective equipment, pre-harvest intervals, restricted entry intervals, buffer zones, spray drift and runoff mitigation measures, handling, manufacture, storage or distribution of a pesticide. If feasible conditions of use that have acceptable risk and value cannot be identified, the pesticide use will not be eligible for registration.

The selected risk management strategy is then implemented as part of the registration decision. The pesticide registration conditions include legally-binding use directions on the label. Any use in contravention of the label or other specified conditions is illegal under the *Pest Control Products Act*. Implementation of post-market decisions follow the framework articulated in the Policy on Cancellations and Amendments Following Re-evaluation and Special Review.[13]

Following a decision, continuous oversight activities such as post-market assessments, monitoring and surveillance, including incident reporting, all play an essential role to help ensure the continued acceptability of risks and value of registered pesticides.

[13] PMRA Regulatory Directive DIR2018-01 *Policy on Cancellations and Amendments Following Re-evaluation and Special Review*.