Registration Decision RD2024-12

DeltaGard SC Insecticide, containing deltamethrin

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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 section of Evaluation approach of this document.

Registration Decision Statement[2] for DeltaGard SC Insecticide

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 DeltaGard SC Insecticide containing the technical grade active ingredient deltamethrin, to control box tree moth on outdoor-grown boxwood.

The Proposed Registration Decision PRD2023-05, *DeltaGard SC Insecticide, containing deltamethrin,* containing the detailed evaluation of the information submitted in support of this registration, underwent a 45-day consultation period ending on 11 August 2023. The evaluation found that, under the approved conditions of use, the health and environmental risks and the value of the pest control product are acceptable. Health Canada received written comments relating to the health and environmental assessments during the public consultation period conducted in accordance with section 28 of the *Pest Control Products Act*.

Comments and responses

Comment in support of this registration

The Canadian Food Inspection Agency expressed support for the registration of DeltaGard SC Insecticide to control box tree moth on boxwood, especially to non-regulated areas of Canada, stating that mechanical removal of box tree moth is not efficient or feasible for commercial production and that there are limited products registered to control this pest.

Comment expressing concern over animal testing

A member of the public mentioned that "Canada recently passed a law to phase out toxicity testing on animals" and noted that cruelty-free alternatives to animal testing exist.

[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.*

Health Canada response

Health Canada requires information on the potential toxic effects of pesticides to determine the potential hazards and risk to human health and the environment from pesticide exposure. Toxicity information typically includes, in part, animal testing data generated by pesticide manufacturers. These studies are conducted according to international testing protocols, which include requirements to ensure protection of the welfare of laboratory animals. While animal toxicity testing currently plays a critical role in assessing human health and environmental risks from exposure to chemical substances, including pesticides, Health Canada supports the reduction of unnecessary animal testing where scientifically justified.

In line with this, the Government of Canada recently introduced amendments to the *Canadian Environmental Protection Act* (CEPA) under Bill S-5 (*Strengthening Environmental Protection for a Healthier Canada Act*) that recognize the need to replace, reduce, or refine the use of vertebrate animal testing when assessing the risks that substances may pose to human health and the environment. These amendments, which received Royal Assent in June 2023, support Health Canada, and Environment and Climate Change Canada in their efforts to promote the development and timely incorporation of alternative methods and strategies, as science permits.

Toward this effort and in line with new requirements introduced through these amendments, Health Canada and Environment and Climate Change Canada will be developing a strategy as part of the Plan of Chemicals Management Priorities to guide their path to replace, reduce or refine the use of vertebrate animals for toxicity testing and assessment under CEPA. Pest control products are regulated under separate legislation, the *Pest Control Products Act*. As such, the recent amendments to CEPA do not apply directly to the regulation of pesticides. However, the strategy currently being developed under CEPA could be applicable, where relevant and possible, to other Government of Canada regulatory programs, including pesticides.

In addition, the *Pest Control Products Act* currently provides sufficient flexibility for Health Canada to take into consideration alternatives to animal testing in the assessment of pest control products. For instance, Health Canada considers whether requirements for animal studies may be waived or addressed with validated non-animal alternatives in hazard assessment when feasible and supported scientifically. In addition, Health Canada issued guidance for industry on the waiving of mammalian acute toxicity studies in 2013 and revised the data requirements for pesticides in 2016 and 2018 to remove the routine requirement for certain animal studies. 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, at what dose level effects may occur, so that this information can then be used to protect human health and the environment. Continued analysis of international trends and approaches is important to ensure continued alignment and harmonization. To this end, Health Canada is an active participant in various international activities aimed at reducing animal testing while ensuring the protection of human health and the environment.

Comments related to consideration of new published literature on the health risks

A non-governmental organization objected to the proposed registration decision for deltamethrin, suggesting that Health Canada needs to fully assess all of the new published literature on the health risks of pyrethroid pesticides registered in Canada.

Health Canada response

Health Canada has conducted a detailed review of the toxicology database for deltamethrin as part of the previous re-evaluation, which is summarized in the Proposed Re-evaluation Decision PRVD2015-07, *Deltamethrin* and Re-evaluation Decision RVD2018-27, *Deltamethrin and its Associated End-use Products*. An update to the hazard assessment for deltamethrin was also conducted as part of the review of Annihilator PolyZone, which was registered for the control of crawling and flying insect pests by application on indoor and outdoor surfaces of agricultural buildings and structures. New information available at the time was considered as part of that update, as outlined in Proposed Registration Decision PRD2019-07, *Deltamethrin and Annihilator PolyZone*, and Registration Decision RD2019-15, *Deltamethrin and Annihilator PolyZone*. An extensive toxicology database is available for the assessment of human health risks of deltamethrin and the data quality is considered adequate to define the majority of the toxic effects that may result from exposure to deltamethrin.

As stated in PRD2023-05, *DeltaGard SC Insecticide, containing deltamethrin* this evaluation was completed under the User Requested Minor Use Label Expansion program, which is a cooperative program between Agriculture and Agri-Food Canada and Health Canada's Pest Management Regulatory Agency, and includes participation by sponsor groups, manufacturers, and both provincial and federal governments. As the new use for deltamethrin is only for the control of box tree moth on boxwood, the dietary risk assessment for deltamethrin will not be impacted. Residential exposure of deltamethrin resulting from this new use will be limited. Given the limited scope of the new use, the hazard assessment relied on previous assessments and did not consider new published literature studies.

Although an updated review of the published literature, subsequent to the issuance of PRD2019-07, was not completed in this current assessment, the literature studies that were referenced in the comments from the non-governmental organization were considered and were determined not to have an impact on the previous hazard assessment (see Appendix I). In addition, any relevant information as it comes to light will be incorporated into future major use expansions and as part of Health Canada's continuous oversight initiative that is currently under development. Assessments by other regulatory authorities were also considered[3,4,5] and no new toxicology data that was not included in the previous Health Canada assessments of deltamethrin

[3] Bellisai, G and al. 2022. Modification of the existing maximum residue level for deltamethrin in maize/corn. EFSA Journal 2022;20(7):7446 doi: 10.2903/j.efsa.2022.7446

[4] Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food 2000. FAO Plant Production and Protection Paper 163. ISSN 0259-2517

[5] Collantes, M and al. 2020. Deltamethrin: Revised Human Health Risk Assessment in Support of Registration Review. USEPA; Document ID EPA-HQ-OPP-2009-0637-0088

was identified. Of note is that the current toxicology reference values established by Health Canada for assessing risks to human health from uses of deltamethrin are generally more protective (lower than) those of other regulatory authorities.

Comments expressing concern over the developmental neurotoxic potential of deltamethrin

A member of the public commented generally that more neurotoxins are not needed in the environment. The commenter also expressed concern that neurotoxic insecticide exposure in utero may play a role in the development of autism.

Additionally, a non-governmental organization commented that there is insufficient certainty that "no harm will occur to human health from exposure" due to the limited number of studies that assess neurobehavioural outcomes in children at levels of deltamethrin to which children in the general population are exposed.

Further comment from a non-governmental organization related to the impact of non-animal or new approach methodologies, including in vitro and physiologically based kinetic models, that should be considered beyond the in vivo data. In particular, a specific study[6] summarizing the results of in vitro testing with deltamethrin was cited in which it was proposed that deltamethrin could have a negative impact on neuronal development, specifically effects on neuronal network formation in rat and human cells, which could result in developmental neurotoxicity.

Health Canada response

As summarized in PRVD2015-07, Health Canada considered several toxicology studies in laboratory animals that address potential neurobehavioural effects of deltamethrin in the young. These studies included various dosing regimens and exposure scenarios, such as single dosing as well as repeated short-term oral dosing of adult animals, prenatal in utero exposure and exposure of the young animal during development in the early-life stages. The extensive toxicology database for deltamethrin allowed Health Canada to thoroughly consider the neurotoxic hazard of deltamethrin to infants and children, as well as potential adverse effects during development. Specifically, the toxicology database for deltamethrin included oral developmental toxicity studies in mice, rats and rabbits; a 2-generation reproductive toxicity study in rats; developmental neurotoxicity (DNT) studies in mice and rats; and an acute oral neurotoxicity study in rats comparing effects in adult and young animals.

Based on a review of the available evidence, Health Canada has noted that the young may be more susceptible to deltamethrin than adults. This potential susceptibility of the young has been accounted for when establishing the conditions of safe use that will ensure exposure to deltamethrin is well below levels of concern.

6 Masjosthusmann, S et al. 2020. Establishment of an a priori protocol for the implementation and interpretation of an in-vitro testing battery for the assessment of developmental neurotoxicity. *EFSA supporting publication* 2020: 17(10): EN-1938. 152 pp. doi: 10.2903/sp.efsa.2020.EN-1938.

In particular, Health Canada selected a study implementing the most sensitive measure of juvenile sensitivity available in the deltamethrin database, the acoustic startle response, to establish the toxicology reference values for relevant exposure scenarios.

In addition, the known susceptibility of the young animal to deltamethrin toxicity was taken into consideration when determining the appropriate assessment factors, including the *Pest Control Products Act* factor, and target margins of exposure. These considerations are detailed in PRVD2015-07.

Therefore, Health Canada has thoroughly considered neurobehavioural outcomes of deltamethrin as well as sensitivity of these outcomes in the young and selected reference values in consideration of these effects. As such, the risk assessment protects against potential sensitivity of the young by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

The in vitro study results cited by the commenter were considered in the weight of evidence for assessing the DNT potential of deltamethrin. The potential for neurotoxic effects on the developing young was identified previously for deltamethrin (see PRVD2015-07) based on results from the available in vivo DNT studies and the acute oral neurotoxicity study comparing effects in adult and young animals. These in vitro study results were referenced as supportive evidence of the in vivo test results in the study cited by the commenter. Furthermore, utilizing in vitro data to support the weight of evidence assessment is consistent with the approach taken in a recent case study developed for the OECD.[7] Here, it was determined that the in vitro study results provided additional mechanistic understanding that could be integrated into the DNT hazard identification and characterization, reducing aspects of uncertainty identified in the in vivo studies. Overall, the developmental neurotoxic potential of deltamethrin is considered to be well characterized for the human health hazard assessment, and the in vitro test results, while contributing to the weight of evidence, did not impact the established health-based reference values.

Comments regarding biomonitoring and epidemiology studies

A non-governmental organization cited a biomonitoring study to support their comment that there was an apparent lack of studies assessing neurobehavioural outcomes in children from exposure to deltamethrin. The commenter stated that Health Canada has not explained how this study was considered in the risk assessment. The commenter also noted that this study demonstrated that pyrethroid urinary metabolites are associated with high levels of behavioural problems. Furthermore, the commenter questioned why Health Canada did not require epidemiology studies as part of its evaluation.

[7] Organisation for Economic Co-operation and Development (OECD) Series on Testing and Assessment No. 362. Case study for the integration of in vitro data in the developmental neurotoxicity hazard identification and characterisation using deltamethrin as a prototype chemical. September, 2022.

Health Canada response

The cited biomonitoring study noted an association between the detection of the pyrethroid metabolites cis-DCCA [3-(2,2-dichlorovinyl)-2,2-dimethylycyclopropane carboxylic acid] and trans-DCCA in urine and impacts on behaviour in children.[8] These two metabolites are degradation products of the pyrethroid active ingredients cypermethrin, cyfluthrin, and permethrin, but not deltamethrin. The cited biomonitoring study did not find any significant associations between behavioural outcomes and urinary levels of the metabolite 3-phenoxybenzoic acid, which is a common metabolite to many pyrethroids, including deltamethrin. As such, this study did not have an impact on the risk assessment for deltamethrin.

Health Canada recognizes the value of epidemiology studies which are considered alongside toxicity studies, as part of the weight of evidence examining the potential toxic effects over various dose levels and exposure scenarios. While Health Canada does not require epidemiology studies, all available epidemiological evidence in the literature is considered. The weight of evidence takes into account whether the studies are designed in a way to be quantitatively or qualitatively relevant in regulatory decision-making. Epidemiological studies may provide valuable insights for potential adverse outcomes in humans; as such Health Canada continues to support the conduct of well-designed epidemiological studies where exposure conditions are well characterized.

Comments regarding cancer and endocrine assessment and established reference doses

A non-governmental organization commented that Health Canada's cancer and endocrine risk assessments are inadequate. They specifically noted that deltamethrin is an endocrine disruptor and that oxidative stress may play a key role in deltamethrin's toxic effects. They further noted that deltamethrin causes "marked toxicity in vertebrates and invertebrates, likely due to oxidative stress, reactive oxidative species (ROS) and reactive nitrogen species (RNS) generation and altered metabolism and resistance." Finally, they stated that there is a lack of robust scientific basis to set human health reference doses given certain properties of deltamethrin, specifically with regards to the associated endocrine disruption potential and evidence of oxidative stress.

Health Canada response

The human health hazard assessment of deltamethrin is based on the review of an extensive toxicology database, as summarized in PRVD2015-07. The scientific merit and toxicological relevance of these studies were thoroughly considered. Animal toxicity studies along with published scientific literature evaluating toxicokinetics, acute effects, neurotoxicity, immunotoxicity, chronic toxicity, carcinogenicity, developmental and reproductive toxicity, as well as other effects that would address concerns for downstream effects from oxidative stress were reviewed. Several in vivo and in vitro genotoxicity studies were also reviewed. Incident reports in humans and animals were also considered.

[8] Oulhote Y, Bouchard MF. 2013. Urinary metabolites of organophosphate and pyrethroid pesticides and behavioral problems in Canadian children. *Environ Health Perspect* 121:1378–1384; doi:10.1289/ehp.1306667.

As outlined in PRVD2015-07, the toxicology database of deltamethrin includes carcinogenicity studies in mice and rats that were conducted according to international standards. In these studies, exposure to deltamethrin did not increase the incidence of tumours in rodents. Further, all of the in vitro and in vivo genotoxicity studies conducted with deltamethrin demonstrated negative results. Given the weight of evidence, it was concluded that there was no evidence of carcinogenicity.

As outlined in PRVD2015-07, the toxicology database of deltamethrin includes reproductive and developmental toxicity studies in rats and/or rabbits that were conducted according to international standards. These studies considered several endocrine-related endpoints that may arise from exposure during sensitive periods of development. These endpoints are considered adequate to define the majority of potential endocrine-mediated effects that may result from exposure to deltamethrin.

Overall, the toxicology reference values account for the adverse health effects seen across the extensive database for deltamethrin. Furthermore, the reference values established by Health Canada for assessing risks to human health from uses of deltamethrin are currently three to fivefold more protective (lower than) than those of other regulatory authorities.

Comment regarding classification of pyrethroids and similarities to other compounds

A non-governmental organization noted the following: “type I and II classification does not reflect the diversity of intoxication signs found following oral administration of various pyrethroids. Pyrethroids act in vitro on a variety of putative biochemical and physiological target sites”

A member of the public noted that deltamethrin seemed similar to neonicotinoids, and a non-governmental organization commented that combined effects on acetylcholinesterase enzymes with potential exposure to methyl carbamates and organophosphates needs to be considered.

Health Canada response

Health Canada recognizes the classification of pyrethroids into type I and type II due to the varying mechanisms of action. However, this classification system of pyrethroids was not used to guide the risk assessment of deltamethrin or other pyrethroids. The toxicology database contains various studies that assess and address the relevant physiologic target sites and any potential intoxication signs, regardless of classification.

Deltamethrin belongs to the pyrethroid class of insecticides, which act primarily by modulating the opening and closing of sodium ion channels. Neonicotinoids are a separate group of pesticides that act by selectively binding and acting at the insect nicotinic acetylcholine receptor. Methyl carbamates and organophosphates act through distinct mechanisms involving inhibition of the acetylcholinesterase enzyme. The chemical structures of pyrethroids, neonicotinoids, and methyl carbamates and organophosphates are also distinct. While these classes of insecticides demonstrated neurotoxic effects, they cause these effects through different mechanisms of toxicity. Pesticides within each class have undergone separate and thorough human health risk assessments that take into account results from compound-specific toxicological databases, as

well as their distinct modes of action. The pesticide classes, or groups of compounds, that make up the pyrethroids, neonicotinoids, methyl carbamates, and organophosphates will be considered as separate clusters of compounds for the assessment of cumulative effects, as per the process described in Science Policy Note SPN2018-02, *Cumulative Health Risk Assessment Framework*.

Comment related to testing of the formulated end-use product.

A non-governmental organization noted that it was unclear what testing was conducted on the formulated product, DeltaGard SC Insecticide.

Health Canada response

With respect to toxicity information on formulated end-use products, the PMRA requires acute toxicity studies to determine the potential hazards from acute exposures. Acute data are used for classification purposes and for the development of appropriate precautionary statements for product labels. Acute studies identify relative acute toxicities by different routes of exposure as well as the potential to produce irritation and sensitization.

The acute toxicity profile of DeltaGard SC Insecticide (Pest Control Product Registration Number 28791) was reviewed when it was first registered for use in Canada in 2007. As noted in PRD2023-05, no changes to the registered formulation of DeltaGard SC Insecticide were proposed as part of the request to register the product for use on outdoor-grown boxwood. The results of acute toxicity testing with DeltaGard SC Insecticide were summarized in PRD2023-05.

The environmental fate and ecotoxicity profile of deltamethrin and DeltaGard SC Insecticide was reviewed when it was first registered for use in Canada in 2007. For details pertaining to environmental fate and ecotoxicology, PRD2023-05 referred the reader to the 2007 review. As the proposed use on outdoor-grown boxwood is within the currently use pattern and there were no changes to the registered formulation of DeltaGard SC Insecticide, no additional environmental data was require to support this application.

Comment related to references listed in Proposed Registration Decision Document PRD2023-05

A non-governmental organization stated that it was unclear how the references identified at the end of PRD2023-05 were considered in the risk assessment.

Health Canada's response:

Two references were listed in PRD2023-05 as information submitted by the applicant. Both of these references were related to the value assessment of DeltaGard SC Insecticide to control box tree moth. These studies are considered in establishing the use pattern as part of the value assessment and were not directly considered in the risk assessments. However, the health and environmental risk assessments are completed based on the use pattern established in the value assessment. For detailed information on PMRA value assessments, please refer to the PMRA Guidance Document, *Value Guidelines for New Plant Protection Products and Label Amendments*, available on Canada.ca.

Comment related to the aggregate assessment compliance

A non-governmental organization commented that it is unclear in Health Canada's evaluation if aggregate assessment requirements were being complied with, or that the assessment was conducted in isolation. The comment indicated that it is not clear in the proposed decision that aggregate risk was included from the proposed new use (on boxwood) along with other uses (food, drinking water, and residential exposure). Furthermore, the commenter claimed that the proposed decision on pyrethrins published in 2020 under PRVD2020-08, Pyrethrins and associated end-use products identified that there were residential uses where no data were available, meaning that existing residential exposure assessments for pyrethroid pesticides appear to be deficient. In addition, the comment stated that cumulative risk was not assessed, since Health Canada has not yet completed the cumulative risk assessment of pyrethroids. Therefore, the comment claims, the proposed decision does not comply with section 7(7)(b)(i) of the Pest Control Products Act.

Health Canada response

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources as well as from all known or plausible exposure routes (oral, dermal, and inhalation). Aggregate exposure to deltamethrin was assessed under the most recent re-evaluation of deltamethrin published in the Proposed Re-evaluation Decision PRVD2015-07. For deltamethrin, exposure via the dermal route was not aggregated because no adverse toxicological effects were noted following repeated dermal dosing. Therefore, the aggregate exposure assessment included scenarios where incidental oral exposure (hand-to-mouth) and chronic dietary exposures are expected to co-occur only. Since the use of deltamethrin on boxwood would result in dermal exposures only, it will not add to the aggregate risks with the residential exposures to deltamethrin that were already assessed under PRVD2015-07.

As noted in the PRVD2020-08 for the re-evaluation of pyrethrins, when there were no data available for the assessment, continued registration was not granted and uses were prohibited, such as some indoor or outdoor application methods for residential applicators. Label statements were added to pyrethrin labels to prevent these uses from occurring. This conclusion was reiterated in the RVD2023-06, *Pyrethrins and Its Associated End-use Products* and is included in the list of risk mitigation measures.

To assess cumulative risk, attention should be focused on exposure estimation for use/pesticide combinations that make up the largest and most important sources of risk (USEPA, 2002).

As discussed in the proposed registration decision, the new use will not impact the dietary contribution and will contribute to limited residential exposure of deltamethrin. Therefore, based on this qualitative assessment of cumulative risk, the contribution of exposure to pyrethroids from the new use is minimal. As such, a cumulative risk assessment of the pyrethroid group is beyond the extent of evaluation required for the use of deltamethrin on boxwood, given the limited scope of the new use.

The cumulative risk assessment of the pyrethroid group will be conducted consistently with the process described in PMRA's framework on cumulative health risk assessment (SPN2018-02).

The aggregate and cumulative risks associated with the use of deltamethrin have been evaluated and the proposed decision for the use of deltamethrin on boxwood is fully compliant with Section 7(7)(b)(i) of the *Pest Control Products Act*.

Comment related to the PMRA's 2015 re-evaluation of deltamethrin (PRVD2015-07)

A non-governmental organization stated the 2015 re-evaluation indicates that levels of concern were exceeded for a variety of terrestrial and aquatic biota including pollinators, birds, and mammals.

Health Canada's response:

The final re-evaluation decision of deltamethrin was published in 2018 (RVD2018-27) and included risk mitigation measures such as precautionary statements and spray buffer zones to protect the environment. Risks to terrestrial and aquatic organisms are acceptable when deltamethrin is used according to label directions.

Comments related to the PMRA's lack of consideration of synergistic and/or cumulative effects of deltamethrin

A non-governmental organization stated that the PMRA did not take into account the synergistic effects or assess the cumulative effects of deltamethrin with other permitted chemicals and registered pesticides.

Health Canada's response:

The PMRA's current environmental risk assessments focus on single active ingredients. While available information on cumulative health effects is considered in the PMRA's health risk assessments under the *Pest Control Products Act* for major regulatory decisions where products have a common mechanism of toxicity, cumulative effects in environmental risk assessments are not currently considered due to lack of information and standard methodologies.

In the context of pesticide registration and re-evaluation, assessing cumulative effects of substances in environmental risk assessments, including potential synergistic effects, is challenging. For example, exposures to pesticides in the environment are highly variable across locations and years, dependent on which crops are grown and which pesticides and rates are used. Estimating exposure for scenarios where organisms can be exposed to multiple pesticides through intentional use at a given application site may be relatively straightforward for some organisms at a small scale (for example, on field, or immediately off-field). However, estimating unintentional exposure, where organisms can be unintentionally exposed to multiple pesticides as residues are transported through the environment and as organisms themselves move through their landscape is much more challenging.

Not all environmental taxa (such as pollinators, birds, mammals, fish, aquatic invertebrates) will be exposed to the same groups and proportions of pesticides due to differences in habitat, diet and life history. Also, in contrast to human health risk assessments, there may be different mechanisms of toxicity of pesticides between taxa considered in the environmental risk assessment.

Given this context, international regulators including the PMRA, the United States Environmental Protection Agency (USEPA) and the European Food Safety Authority (EFSA) currently focus on cumulative health risk assessments.

Despite these challenges, the assessment of cumulative environmental effects is of global interest. As outlined in the Notice of Intent NOI2023-01, Strengthening the regulation of pest control products in Canada, the PMRA is proposing to amend the Pest Control Products Regulations to require the Minister to consider the cumulative effects on the environment of pesticides that have a common mechanism of toxicity, where information and methodology are available. Additionally, the amendments would give the Minister explicit authority to require registrants and applicants to submit available information on cumulative environmental effects, so this information could be considered within the PMRA's environmental risk assessments. In cases where the information and methodology are available, regulatory decisions would be informed by an evaluation of cumulative environmental effects, thereby improving the protection of the health and environment of Canadians.

The PMRA is in the initial stages of developing a draft framework to assess cumulative effects of pesticides on the environment, which will include potential synergistic effects. In moving forward, the PMRA will collaborate with other jurisdictions, experts, and other governmental department partners such as Environment and Climate Change Canada. In October 2023, the PMRA began initial conversations with the Science Advisory Committee on Pest Control Products (SAC-PCP), seeking advice on first steps in developing such a framework.

Comment related to species sensitivity distribution

A non-governmental organization stated the PMRA's risk assessment even when refined to lower levels of concern still permits a species sensitivity distribution that, even if levels of concern are not exceeded, permits harm to 5% of species – which is not authorized under the *Pest Control Products Act*.

Health Canada's response:

The *Pest Control Products Act* establishes criteria for determining the acceptability of environmental risk associated with pest control products. This determination hinges on the reasonable certainty that such products, considering their conditions of registration, will not harm the environment. The environmental risk assessment involves a systematic scientific evaluation of pesticide fate and hazard to non-target organisms. Detailed guidance on Health Canada's approach to this assessment, as well as the protection goals used to prevent unacceptable risks to the environment, are outlined in the PMRA Guidance Document titled *Health Canada's Approach to Environmental Risk Assessment for Pest Control Products.*

The PMRA uses a tiered environmental risk assessment approach. The first tier, known as a screening level risk assessment, uses scientific data (for example, standard studies describing fate, behaviour and hazards) and conservative assumptions to identify pesticides that pose a negligible environmental risk. If a potential risk is identified, higher-tier assessments are conducted. Compared to the screening level, higher tiers of the environmental risk assessment incorporate more realistic information on exposure and toxicity. The protection goals used in the environmental risk assessment remain the same as the risk assessment is refined.

In the re-evaluation of deltamethrin (PRVD2015-07/RVD2018-27), the level of concern in the screening-level risk assessment was exceeded for marine invertebrates. A species sensitivity distribution (SSD) analysis was conducted to produce a refined effects metric. An SSD model produces HC_x estimates, where HC stands for hazardous concentration. The subscript, x, is a percentage value, and the HC_x is the concentration of the chemical of concern at which x% of species are estimated to have their toxicity endpoint exceeded (or met, in the case of the x-percentile species). Then, by definition, the species whose toxicity endpoints are not expected to be exceed at the HC_x is 100-x% of species. Conventionally, an HC_5 value is used as an effects metric for addressing protection goals associated with the community level.

The use of the SSD in the refined assessment is consistent with the PMRA's goal to protect aquatic invertebrates at the community level.

Comments related to label mitigation

A non-governmental organization stated the most recent environmental risk assessment for deltamethrin products fails to establish that there is reasonable certainty that no harm will occur to the environment. Therefore, the PMRA is not in the position to authorize the deltamethrin use expansion on boxwood. Furthermore, they state that the PMRA has failed to explain how mitigation measures on the label will protect a wide range of biota from the effects of deltamethrin.

Health Canada's response:

As noted in the response to the comment related to species sensitivity distributions, the *Pest Control Products Act* establishes criteria for determining the acceptability of the environmental risk associated with pest control products. The conditions of registration (in other words, label instructions) are considered when determining the acceptability of environmental risk. The environmental risk assessment for deltamethrin in PRD2023-05 was conducted as outlined in the PMRA Guidance Document titled *Health Canada's Approach to Environmental Risk Assessment for Pest Control Products.*

The major new use of deltamethrin for the control of box tree moth on outdoor-grown boxwood trees applies broadly to the active ingredient, deltamethrin, and specifically to the registered end-use product, DeltaGard SC Insecticide (Reg. No. 28791). The maximum cumulative application rate for the control of box tree moth is within the currently registered rate for deltamethrin.

As such, the environmental risk assessment from PRVD2015-07/RVD2018-27 is protective of the use of deltamethrin to control box tree moth, with the exception of spray drift from airblast application. Airblast is a new application method with different spray drift considerations than field sprayer or aerial application methods.

When the PMRA identifies potential environmental risks from pesticides, risk mitigation measures are used to reduce potential exposure and risks to non-target organisms. Various measures can be employed to reduce risks depending on the type and magnitude of concern.

These measures can include label statements to identify hazards and mitigate risks, changes to how the pesticide is used, or cancellation of some, or all, uses. These measures are intended to inform users of hazards and best practices, and implement restrictions to decrease exposure (and hence risk) of non-target organisms.

In the case of deltamethrin, a number of risk mitigation measures are employed:

- Label statements to indicate toxicity to bees, beneficial insects, mammals and aquatic organisms;
- Instructions on when, and how, to apply deltamethrin to minimize exposure from direct application or runoff to the above organisms; and,
- Spray buffer zones of up to 120 meters to minimize spray drift to terrestrial and aquatic habitats downwind from the sites of applications.

In addition to the existing risk mitigation measures on the label of DeltaGard SC Insecticide, PRD2023-05 proposed the following risk mitigation measures for use of the product to control box tree moth:

- Spray buffer zones of up to 85 meters to protect terrestrial and aquatic habitats when airblast application is used; and,
- Updating label language to mitigate risk to pollinators to be consistent with current standards.

The above labelling requirements and mitigation measures, including spray buffer zones, are expected to be protective of non-target terrestrial and aquatic organisms. Environmental risks from the use of deltamethrin for the control of box tree moth are acceptable when DeltaGard SC Insecticide is used according to label directions. The approved labels for pest control products are legal documents that govern a pesticide's use. It is prohibited to use a pesticide in a manner that is inconsistent with the label directions.

Comments related to reliance on monitoring or modelling

A non-governmental organization stated that given how limited historic use of deltamethrin is, better monitoring or reliance on modelling is needed if additional use expansions are granted. They also noted that the assessment of the potential risk to aquatic organisms using EECs based on surface water monitoring could not be conducted that addresses the proposed new boxwood use.

Health Canada's response:

Since the previous risk assessment for deltamethrin (PRVD2015-07/RVD2018-27) was published, the availability of water monitoring data to the PMRA has improved, especially with the onset of Health Canada's pilot program for a long-term, collaborative national-scale Water Monitoring Program for Pesticides (NWMPP) in 2022. Although deltamethrin was not included as one of the analytes in the NWMPP pilot due to issues with the analytical method, a new analytical method is being developed so that it can be included in future years. Despite it not being present in the NWMPP's analyte list, surface water monitoring data for deltamethrin are available from many provincial government public databases, including Alberta, Ontario, Quebec, and Prince Edward Island (PEI).

The available deltamethrin surface water samples collected between 1 January 2015, and 28 September 2023, are summarized in Table 1.

Since the publication of the last risk assessment, there were 2196 surface water samples analyzed for deltamethrin from six provinces. Approximately 60% of these samples came from Alberta (1286 out of 2196 samples), with Ontario being the next highest representative province at just over 30% (706 samples), with Quebec (117 samples), Prince Edward Island (33 samples), Nova Scotia (30 samples), and New Brunswick (24 samples) also being represented. Out of these 2196 samples, there were a total of six (< 0.01%) detections, with a maximum detection of 0.063 µg/L. All of the detects came from Alberta in 2015 (2), 2018 (2), and 2019 (2). Both detects in 2018 (0.008 µg/L and 0.01 µg/L in North Saskatchewan River) and one in 2019 (0.008 µg/L in Bow River) were just above the detection limit of 0.007 µg/L. The remaining three detections were 0.051 (once in each of two unknown irrigation canals in 2015) and 0.063 (in South Saskatchewan River in 2019) µg/L.

Table 1 Summary of deltamethrin detections in Canadian surface water sources based on available data collected from 2015 to 2023 (accessed on 28 September 2023)

Data source	Number of samples	Number of sample detects	Percentage of detections (%)	LOD range (µg/L)	Maximum concentration measured (µg/L)
Alberta (2015–2016, 2018–2023)	1286	6	<0.01	0.007–0.040	0.063
New Brunswick (2015)	24	0	0	0.003	n/a
Nova Scotia (2015)	30	0	0	0.003	n/a
Ontario (2015-2020)	706	0	0	NR	n/a
Prince Edward Island (2015, 2018)	33	0	0	0.003–0.025	n/a
Quebec (2015–2016)	117	0	0	0.080	n/a
Canada (2013–2020)	**2196**	**6**	**<0.01**	**0.003–0.080**	**0.063**

LOD: Level of Detection; NR: not reported

Of the three crops chosen for water modelling in the previous risk assessment (PRVD2015-07), apples are grown most in Ontario (39%), with Quebec and British Columbia coming in joint second (27%; Statista, 2019), broccoli is predominantly grown in Quebec (64%), with Ontario in second (23%; AAFC, 2005), and corn is grown predominantly in Ontario (62%), with Quebec coming in second (30%; Stats Can, 2015). Most of the deltamethrin samples, including all six detections, came from Alberta, which is not a large producer of these crops. Ontario and Quebec are the top two producers for all three crops and have 823 water samples between them, resulting in no detections. Albeit, the detection limits in these two provinces were either not reported or were 0.08 µg/L, which is above many of the aquatic effects metrics used in the risk assessment.

While these samples do not represent a robust monitoring data set for Ontario and Quebec, the fact that there were no detections provides weight to the decision to allow the boxwood minor use expansion as the use pattern for boxwoods is below the currently registered maximum rate for deltamethrin.

Comments related to species at risk

A non-governmental organization stated the PMRA has not assessed the effects of deltamethrin on species at risk.

Health Canada's response:

Under the *Pest Control Products Act*, "environment" encompasses biodiversity and wildlife, including species at risk. In protecting species at risk, the PMRA currently takes a layered approach. Firstly, the environmental risk assessment is conservative in its determination of effects on organisms, including by considering the most sensitive organisms, and through the application of uncertainty factors to build in a margin of protection. Additionally, when there are concerns for a particular species at risk through use of a pesticide, this is considered and incorporated into the environmental risk assessment and mitigation measures.

Moreover, the *Pest Control Products Act* requires that notices be sent to all provinces, territories, and other relevant federal departments when re-evaluations or special reviews are initiated, to request information related to health or environmental risks or value. It further requires these groups be consulted prior to any major regulatory decision being made. Information provided to the PMRA in response to such notices can include information on wildlife and species at risk, particularly from our federal partners at Environment and Climate Change Canada (ECCC) and the provinces and territories.

Lastly, pesticide users are required to respect provisions of other legislation that are implicated when using pesticides, notably the *Species at Risk Act* (SARA) and *Fisheries Act*.

Other information

The relevant confidential test data on which the decision is based (as referenced in PRD2023-05, *DeltaGard SC Insecticide, containing deltamethrin)* 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.

Any person may file a notice of objection[9] 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 and pest management portion of the Canada.ca website (Public Engagement Portal – Public Engagement Forms – Notice of Objection) or contact the PMRA's Pest Management Information Service.

[9] 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 there is acceptable risk to human health and the environment, taking into account the conditions of registration.

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.

Premarket 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.[10]

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.[11] 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.[12]

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.[13]

Assessments estimate potential health risks to defined populations[14] 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

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

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

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

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

14 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*.

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.

List of abbreviations

♂	male
♀	female
↑	increased
↓	decreased
ADI	acceptable daily intake
ALT	alanine aminotransferase
AUC	area under the curve
BMC	benchmark concentration
bw	body weight
C/EBP	CCAAT (cytosine-cytosine-adenosine-adenosine-thymidine) enhancer-binding protein
CFIA	Canadian Food Inspection Agency
CM	classification model
COX2	cyclooxygenase-2
CYP2E1	cytochrome P450 family 2 subfamily E member 1
DBCA	3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid
DCCA	3-(2,2-dichlorovinyl)-2,2-dimethylycyclopropane carboxylic acid
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
ECM	extracellular matrix
ER	endoplasmic reticulum
GC-NCI-MS	gas chromatography-negative chemical ionization-mass spectrum
GI	gastrointestinal
GRP78	glucose-regulated protein 78
IATA	integrated approaches to testing and assessment
IV	intravenous
IVB	in vitro testing battery
kg	kilogram(s)
LOAEL	lowest observed adverse effect level
MDA	malondialdehyde
mg	milligram(s)
mL	millilitre
MWM	Morris Water Maze
NO	nitric oxide
NOAEL	no observed adverse effect level
OR	odds ratio
p66shc	p66 src homologous-collagen homologue
PBA	phenoxybenzoic acid
PBK	physiologically based kinetic
PMRA	Pest Management Regulatory Agency
POD	point of departure
PRD	proposed registration decision
PRVD	proposed re-evaluation decision
qPCR	quantitative polymerase chain reaction
RNA	ribonucleic acid
RNS	reactive nitrogen species

ROS	reactive oxygen species
TAC	total antioxidant capacity
TP53	tumour protein 53
wt	weight

Appendix I

Summary of published literature studies cited in comments Received for PRD2023-05, DeltaGard SC Insecticide (Submission 2021-2702)

The studies summarized in the Appendix I, Table 1 below were cited in comments received for PRD2023-05 and were deemed to have some relevance to the human health hazard assessment of deltamethrin. These studies were screened for acceptability according to Health Canada guidance, the study methods described within were analyzed, and the key findings were summarized.

These studies were classified as "acceptable with limitations" as they were considered supplemental in nature for various reasons, such as the study design was limited to a single dose level preventing the assessment of a dose response, or other limitations in the study design hindered its utility. Overall, the results of these studies did not impact the previous hazard assessment of deltamethrin as the identified endpoints or potential downstream effects were adequately captured in the existing hazard assessment, or the existing toxicology reference values provide an adequate margin to the dose levels at which effects were reported.

Several additional studies related to toxicity or the identification of potential hazards that were cited in the comments to PRD2023-05 were not included in this table due to lack of relevance to the hazard assessment. These additional studies were not considered in the hazard assessment as they were conducted with deltamethrin formulations or combinations of deltamethrin with another compound (therefore the noted effects cannot be attributed specifically to deltamethrin), used methods of administration that are of little relevance to human exposure scenarios (intraperitoneal or subcutaneous injection), studies conducted on mosquito nets, review papers that summarized results from other primary sources (key studies that were cited in the review papers that were deemed to have some relevance to the hazard assessment are included in the table below), documents that are not peer-reviewed literature studies, general guidance documents and resources, and other review papers with no dose levels or endpoints relevant to the hazard assessment.

Table 1 Summary of relevant published literature studies

Study type/Study Title/Study authors/ Animal (if relevant)/ PMRA No.	Purity/ Group size/ Exposure/Additional study description	Study results
Studies investigating oxidative stress (non-guideline)		
30-day oral toxicity (gavage) Influence of green tea extract on oxidative damage and apoptosis induced by deltamethrin in rat brain Albino rats Ogaly, H.A., et al, 2015 (cited in review paper by	Purity >99% 0 (0.2 mL corn oil only), 0.6 mg/kg bw/day in corn oil for 30 days **Note:** other groups received, green tea or green tea and deltamethrin (results not reported here)	**Acceptable with limitations** (only one dose level tested) **0.6 mg/kg bw/day:** ↑ oxidative stress parameters (MDA, NO), ↓ antioxidant capacity (TAC), ↑ DNA fragmentation, ↑ DNA laddering, ↑ markers of DNA damage, ↑ cells immunopositive for COX2 and P53, ↑ apoptotic genes (TP53, COX), central chromatolysis, neuronal swelling, cell membrane lysis, shrunken neurons, degeneration and necrosis of neurons with gliosis and marked vacuolation of brain neuropil, degenerated cerebella Purkinje cells, neurophagia.

Study type/Study Title/Study authors/ Animal (if relevant)/ PMRA No.	Purity/ Group size/ Exposure/Additional study description	Study results
Chrustek, A., et al, 2018, PMRA No. 3613495) PMRA No. 3613496	12 ♂/group Testing included oxidative stress parameter assay, DNA damage evaluation, DNA fragmentation percentage, DNA laddering assay, Comet assay, apoptotic gene expression analyses, and histopathological analysis of the brain. Animals were sacrificed at the end of the dosing period and brain tissue was collected for analyses.	
Prenatal placental transcriptome study (gavage) Effects of prenatal pesticide exposure on the fetal brain and placenta transcriptomes in a rodent model C57BL/6J mice Lesseur, C. et al., 2023 PMRA No. 3613501	Purity: not reported 0, 3 mg/kg bw/day in corn oil Maternal animals: 19 ♀ in the control group, 12♀ in the deltamethrin group Fetal brain samples pooled from some dams, yielding 18 litters in the control group, 8 litters in the deltamethrin group Maternal animals were dosed every 3 days for 2 weeks prior to breeding and until gestational day 17 and were sacrificed at the end of the study. Fetal brain and placental samples were obtained. RNA sequencing was conducted to obtain transcriptomes. Weighted gene co-expression networks, differential expression, and pathway analyses were conducted, and 14 brain gene co-expression modules were identified.	**Acceptable with limitations** (only one dose level tested) **3 mg/kg bw:** impacted genes in calcium signaling, spliceosome, and extracellular matrix interaction pathways

Study type/Study Title/Study authors/ Animal (if relevant)/ PMRA No.	Purity/ Group size/ Exposure/Additional study description	Study results
7-day oral toxicity study (gavage) The implication of p66shc in oxidative stress induced by deltamethrin Sprague Dawley Rats Ding, R., et al., 2017 PMRA No. 3613502	Purity 98.2% 0, 2, 5, 10, 20, or 40 mg/kg bw/day in corn oil for 7 days 7 ♂/group 4h after dosing, mortality, BW, and general adverse effects were monitored. Animals sacrificed, blood collected and analyzed, histopathological examinations conducted. Cytosolic superoxide generation, cell culture, ROS generation, Western blot analysis, Immunofluorescence, plasmid construction and cell transfection, and RNA interference measures also conducted. p66shc is an isoform of an adaptor protein that has been proved to play a crucial role in oxidative stress-induced mitochondrial alterations and modulation of reactive oxygen species production	**Acceptable with limitations** (study results propose a mechanistic pathway underlying toxic effects of deltamethrin) **≥2 mg/kg bw/day:** hemorrhage of oral, nasal cavity and canthus, ↑ cytosolic superoxide in brain, liver, heart, ↑ p66shc in heart **≥5 mg/kg bw/day:** writhing movements of limbs and trunk, asthenia, anorexia, ↑ BW (except 20 mg/kg bw/day group), slight kidney damage, ↑ neutrophil percentage, **≥10 mg/kg bw/day:** coarse whole body tremors, degenerated renal tubules, intraluminal exfoliation with granular cast formation, congestion of kidney blood vessels, enlarged and congested renal veins, cellular debris in in tubular lumen, shrunken glomerulus, degenerated Bowman's capsule with wide cellular space and cellular debris, dilated and congested central veins of the liver, altered architecture of hepatocytes, vacuolization of cytoplasm of hepatocytes, ↑ ALT, ↑ p66shc in brain and liver **40 mg/kg bw/day:** mortality on Day 2 (100%) In vitro portion of study showed increased ROS and p66shc cell line expression
30-day oral toxicity (gavage) Hippocampal ER Stress and Learning Deficits Following Repeated Pyrethroid Exposure C57BL/6 Mice (♂) Hossain, M. et al., 2015 PMRA No. 3613519	Purity 99% 0, 3 mg/kg bw/day in corn oil every 3 days for 60 days **Note:** 3-day dosing interval chosen for the clearance of deltamethrin from the body 17 ♂/group After the dosing period, animals were assigned to 4 groups for different analyses. Behavioural (Morris water maze) (n=6), biochemical	**Acceptable with limitations** (only one dose level tested) **3 mg/kg bw/day**: ↑ hippocampal C/EBP-homologous protein, ↑ hippocampal GRP78, ER-stress mediated apoptosis (↑ hippocampal caspase-12 and activated caspase-3, ↑ number of cleaved caspase-3 immunoreactive cells in dentate gyrus), impaired learning/acquisition in MWM, ↓ cell proliferation in dentate gyrus

Study type/Study Title/Study authors/ Animal (if relevant)/ PMRA No.	Purity/ Group size/ Exposure/Additional study description	Study results
	(Western blot analysis) (n=5), immunohistochemical (n=3), neurogenesis (n=3).	
30-day oral toxicity study (gavage) Vitamin E attenuates neurotoxicity induced by deltamethrin in rats Albino rats (strain not specified) Galal, M.K., et al., 2014 (cited in review paper by Lu, Q., et al, 2019 PMRA No. 3613526) PMRA No. 3613525	Purity >99% 0 (1 mL/kg bw corn oil) or 0.6 mg/kg bw/day in corn oil for 30 days 10 ♂/group **Note:** other groups received, vitamin E or vitamin E and deltamethrin (results not reported here) Testing included biochemical analysis, DNA fragmentation assay, qPCR, DNA laddering assay, Comet assay, apoptotic gene expression analyses, and histopathological analysis of the brain. Animals were sacrificed at the end of the dosing period and brain tissue was collected for analyses.	**Acceptable with limitations** (only one dose level tested) **0.6 mg/kg bw/day:** ↑ lipid peroxidation, nitric oxide concentration, DNA fragmentation, CYP2E1, TP53, COX2, ↓ antioxidant capacity.
Physiologically based kinetic (PBK) models and DNT IVB (non-guideline)		
Physiologically based kinetic (PBK) model Considering developmental neurotoxicity in vitro data for human health risk assessment using physiologically based kinetic modeling: deltamethrin case study Maass, C. et al., 2023 PMRA No. 3613499	To compare human fetal brain concentrations to in vitro DNT benchmark concentration, PBK model created by PK-Sim (version 9). Deltamethrin properties sourced from literature, internal company data, and in vivo and in vitro rat data. Model was then translated to human in vivo exposure Human fetal brain exposure after maternal exposure to deltamethrin was estimated. Read-across approach used to estimate blood-placenta partitioning range.	**Acceptable with limitations** (study does not provide information regarding endpoints for use in quantitative risk assessment) **Summary of key findings:** The model demonstrated that deltamethrin transfer across blood brain barrier is limited, resulting in a maternal plasma/brain concentration ratio ≈ 0.06 determined from species extrapolation of rat data. The worst-case scenario of fetal/maternal plasma ratio was estimated to be 1.2 (based on a median of read-across chemicals). Modelled human fetal brain concentrations were far below the in vitro benchmark level of the DNT-IVB.

Study type/Study Title/Study authors/ Animal (if relevant)/ PMRA No.	Purity/ Group size/ Exposure/Additional study description	Study results
Physiologically based kinetic (PBK) model with in vivo toxicokinetic testing (gavage and IV, non-guideline) Physiologically Based Pharmacokinetic Modeling of Deltamethrin: Development of a Rat and Human Diffusion-Limited Model Long Evans rats Godin, S.J., et al., 2010 PMRA No. 3613511	98.9% purity A PBK model was used to describe gastrointestinal absorption (mediated by phase III efflux transporters pumping deltamethrin out of enterocytes into GI tract). In vivo analyses of dose-dependence of absorption and bioavailability were conducted to assess predictions of the PBK model. The model was optimized, sensitivity analysis was conducted, and then predictions were extrapolated to humans. 0.3 and 3.0 mg/kg bw administered in corn oil (1 mL/kg bw) 4 ♂/group Animals were sacrificed, histopathological analyses were conducted. Another group received 1 mg/kg bw deltamethrin via IV, bioavailability was calculated by comparing the oral administration and IV groups. Deltamethrin sources from literature and in vitro data were used to translate human in vivo exposure based on a dose level of 1 mg/kg bw/day. Human fetal brain exposure after maternal exposure to deltamethrin was estimated. Read-across approach used to estimate blood-placenta partitioning range	**Acceptable with limitations** (study does not provide information regarding endpoints for use in quantitative risk assessment) **Summary of key findings:** There was no difference in bioavailability between both dose levels. Dose-dependence of oral absorption not observed in vivo, unlike what PBK model predicted. Biphasic distribution in the blood and brain was apparent following IV administration. Diffusion-limited mode accurately depicts rapid decrease of liver concentrations and brain concentrations for the 3.0 mg/kg bw dose level. Predicted brain $AUC_{0-48\ h}$ of deltamethrin in humans was threefold greater than in rats.
DNT IVB Assays Establishment of an a priori	Human and rat cell-based in vitro test battery of DNT assays.	**Acceptable with limitations** (study does not provide information regarding endpoints for use in quantitative risk assessment; potential DNT effects covered by

Study type/Study Title/Study authors/ Animal (if relevant)/ PMRA No.	Purity/ Group size/ Exposure/Additional study description	Study results
protocol for the implementation and interpretation of an in-vitro testing battery for the assessment of developmental neurotoxicity Masjosthusmann, S. et al., 2020 PMRA No. 3613533	Fit-for-purpose evaluation considered 4 key criteria: test system, exposure scheme, assay and analytical endpoint(s), classification method. Challenged with 119 chemicals (with extensive toxicology database) in 5 test systems, assessing 10 DNT-relevant endpoints and 9 viability/cytotoxicity endpoints. Deltamethrin selected as compound for case study to show how these data may be used within an IATA for regulatory decisions. Comparison of effects leading to BMC in various assays in battery and applied CM for data. ToxPies and DNTPies presented. Aimed to assess how results of the battery could improve risk assessment when used together with other available data.	existing in vivo toxicology database) **Summary of key findings:** Neuronal network formation assay indicates deltamethrin effects on rat NNF (neuronal network formation) and NPC5 (oligodendrocyte differentiation). Deltamethrin effects on human NNF and NCC migration (UKN2) were less potent, occurring at higher dose levels (1-2× higher). Effects also observed on rat synaptogenesis, rat neurite maturation, human neurite length (NPC4) and area (NPC4, UKN5) and radial glia migration (NPC2a) at higher concentrations (nonspecific, cannot be distinguished from effects on cell viability)
Human biomonitoring, epidemiology, or case studies		
Human biomonitoring study Pyrethroids in human breast milk: Occurrence and nursing daily intake estimation Corcellas C., et al., 2012 PMRA No. 3613515	Breast milk samples collected from mothers in Brazil (20 samples), Colombia (27 samples), and Spain (6 samples) between 2009–2010. Participants resided in urban, industrial, and rural areas. Three archived samples from 2003–2006 were also included in analyses. 10–50 mL samples were analyzed, mothers also self-reported use of pesticides at home, maternal age, parity, newborn weight and sex. GC–NCI–MS–MS	**Acceptable with limitations** (study does not provide information regarding endpoints for use in quantitative risk assessment) **Summary of key findings:** Deltamethrin samples in breastmilk ranged from 0.09 ng/ g liquid wt to 1.86 ng/g liquid wt; some samples were non-detects. The intake levels of nursing infants were estimated to be 0.07 to 1.3 µg/ kg bw/day of deltamethrin.

Study type/Study Title/Study authors/ Animal (if relevant)/ PMRA No.	Purity/ Group size/ Exposure/Additional study description	Study results
	analyses determined levels of pyrethroid in these samples including deltamethrin	
Human epidemiology and biomonitoring study Urinary Metabolites of Organophosphate and Pyrethroid Pesticides and Behavioural Problems in Canadian Children Oulhote, Y., et al., 2013 PMRA No. 3613516	To assess potential associations between pyrethroid exposure and behavioural problems in children, Canadian Health Measures Survey (2007-2009) results were used. This included self-reported information on demographics and health history. Blood and urine samples were collected. Results of children aged 6-11 (N=1081) were analyzed. Strengths and Difficulties Questionnaire (SDQ) was administered. Odds ratios were estimated using logistic regression to identify associations between urinary metabolites of pyrethroids with behavioural outcomes. Levels of other pyrethroid metabolites as well as organophosphates were evaluated but are not reported here due to lack of relevance.	**Acceptable with limitations** (study does not provide information regarding endpoints for use in quantitative risk assessment; potential DNT effects covered by existing in vivo toxicology database) **Summary of key findings:** Concentrations of the metabolite 3-PBA were not significantly associated with learning outcomes (ORs for outcomes ranges from 0.7 to 1.3). The association between 3-PBA levels and conduct disorder scores were higher in girls than boys, but there was no statistical significance.
Human epidemiology and biomonitoring study Pyrethroid insecticide exposure and cognitive developmental disabilities in children: The PELAGIE mother–child cohort Viel, J.F., et al., 2015 PMRA No. 3613534	Cohort of pregnant women (N=3421) from Brittany, France (2002–2006), and 287 mothers agreed to cognitive assessment of their children when they reached 6 years of age. Mothers completed questionnaire of sociodemographic information. Urinary metabolites measured in mothers between 6–19 gestational weeks, and then in children at age 6.	**Acceptable with limitations** (study does not provide information regarding endpoints for use in quantitative risk assessment; potential DNT effects covered by existing in vivo toxicology database) **Summary of key findings:** There was no consistent correlation between maternal prenatal pyrethroid metabolite concentrations and children's cognitive scores. Low-level childhood exposures to deltamethrin (as cis-DBCA is its principal and selective metabolite), in particular, and to pyrethroid insecticides, in general (as reflected in levels of the 3-PBA metabolite) may negatively affect neurocognitive development by 6 years of age. Childhood 3-PBA and cis-DBCA (deltamethrin metabolites) concentrations were both negatively associated with verbal comprehension scores and with working memory scores.

Study type/Study Title/Study authors/ Animal (if relevant)/ PMRA No.	Purity/ Group size/ Exposure/Additional study description	Study results
	Neuropsychological follow up to assess verbal comprehension and working memory using the Wechsler Intelligence Scale for Children: Associations between maternal and child urinary metabolites with cognitive outcomes were calculated.	
Human epidemiology and biomonitoring study Determinants of children's exposure to pyrethroid insecticides in western France Glorennec, P. et al., 2017 PMRA No. 3613535	Follow up study to the PELAGIE mother–child cohort (reviewed above, PMRA No. 3613534). Urinary metabolites of pyrethroids measured in 6-year-old children (N=245) from Brittany, France (2009–2012) as well as dust samples from homes. Mothers reported sociodemographic information and insecticide use. Dietary exposure sources from food frequency questionnaire completed by a parent. Literature review conducted to determine potential determinants of exposure. Other metabolites not associated with deltamethrin were reviewed but are not reported here due to lack of relevance.	**Acceptable with limitations** (study does not provide information regarding endpoints for use in quantitative risk assessment; potential DNT effects covered by existing in vivo toxicology database) **Summary of key findings:** Deltamethrin was detected in 15% of dust samples in the home. Deltamethrin metabolites were detected in 16–84% of urinary samples. Dietary habits were most consistently associated with urinary metabolite levels. Fruit consumption was most associated with 3-PBA levels, cereal was most associated with cis-DBCA, and semolina was most associated with F-PBA levels. Parent working with pesticides was associated with 3× higher urinary metabolite levels in kids.
Studies investigating effects on male reproductive tissues (non-guideline)		
1-generation reproductive toxicity (gavage) Embryonic exposure to dimethoate and/or deltamethrin impairs sexual development and programs reproductive success in adult male offspring mice Swiss Albino mice	0 or 5 mg/kg bw/day in corn oil 5 ♀/group Pregnant mice dosed from pregnancy Day 3–21. Fertility and reproductive endpoints measured in male offspring in adulthood.	**Acceptable with limitations** (only one dose level tested) **5 mg/kg bw/day:** ↓ testes wt, ↓ sperm density, motility, and vitality, ↑ abnormal sperm

Study type/Study Title/Study authors/ Animal (if relevant)/ PMRA No.	Purity/ Group size/ Exposure/Additional study description	Study results
Slima, A.B., et al., 2011 PMRA No. 3613521	Two other groups were dosed with dimethoate, and a combination of deltamethrin and dimethoate; results not reported for these groups	
35-day ♂reproductive toxicity (gavage) Endocrine disrupting potential and reproductive dysfunction in male mice. Swiss Albino mice (♂) Slima, A.B., et al., 2017 PMRA No. 2967885	Purity 98% 24 ♂/group 0 (distilled water) or 5 mg/kg bw/day deltamethrin ♂ were then mated with untreated ♀ to produce offspring. Evaluation of ♂ mating and fertility indices, sperm abnormalities, serum reproductive hormone levels (testosterone and inhibin B), histopathological examination of the testes.	**Acceptable with limitations** (only one dose level tested) **5 mg/kg bw/day:** ↓ mating index and fertility index in ♂ mice, ↓ in the number of pregnant ♀ and number of litters, ↓ semen ejaculate volume, ↓ sperm count, ↓ sperm motility, ↓ viability, ↑ abnormal sperm, ↓ testosterone and inhibin B levels, alterations of the seminiferous tubules, sloughing of germ cells into tubular lumen, ↑ vacuolization of germ cells cytoplasm, disruption of spermatogenic cells, atrophy of seminiferous tubules with a subsequent ↑ in the interstitial space.

Reference list of studies in Appendix I, Table 1

PMRA Document Number	Reference
3613495	Chrustek A, Hołyńska-Iwan I, Dziembowska I, et al. Current Research on the Safety of Pyrethroids Used as Insecticides. Medicina (Kaunas). 2018;54(4):61. Published 2018 Aug 28. doi:10.3390/medicina54040061. DACO 4.8
3613496	Ogaly HA, Khalaf AA, Ibrahim MA, Galal MK, Abd-Elsalam RM. Influence of green tea extract on oxidative damage and apoptosis induced by deltamethrin in rat brain. Neurotoxicol Teratol. 2015;50:23-31. doi:10.1016/j.ntt.2015.05.005. DACO 4.8
3613499	Maass C, Schaller S, Dallmann A, Bothe K, Müller D. Considering developmental neurotoxicity in vitro data for human health risk assessment using physiologically-based kinetic modeling: deltamethrin case study. Toxicol Sci. 2023;192(1):59-70. doi:10.1093/toxsci/kfad007. DACO 4.8
3613501	Lesseur C, Kaur K, Kelly SD, et al. Effects of prenatal pesticide exposure on the fetal brain and placenta transcriptomes in a rodent model. Toxicology. 2023;490:153498. doi:10.1016/j.tox.2023.153498. DACO 4.8
3613502	Ding R, Cao Z, Wang Y, et al. The implication of p66shc in oxidative stress induced by deltamethrin. Chem Biol Interact. 2017;278:162-169. doi:10.1016/j.cbi.2017.10.005. DACO 4.8
3613511	Godin SJ, DeVito MJ, Hughes MF, et al. Physiologically based pharmacokinetic modeling of deltamethrin: development of a rat and human diffusion-limited model. Toxicol Sci. 2010;115(2):330-343. doi:10.1093/toxsci/kfq051. DACO 4.8
3613533	Masjosthusmann S., Blum J., Bartmann K., Dolde X., Holzer A., Stürzl L., Keßel E. H., Förster N., Dönmez A., Klose J., et al. (2020). Establishment of an a priori protocol for the implementation and interpretation of an in-vitro testing battery for the assessment of developmental neurotoxicity. EFS3 17, 1938E. DACO 4.8
3613515	Corcellas C, Feo ML, Torres JP, et al. Pyrethroids in human breast milk: occurrence and nursing daily intake estimation. Environ Int. 2012;47:17-22. doi:10.1016/j.envint.2012.05.007. DACO 4.8
3613516	Oulhote Y, Bouchard MF. Urinary metabolites of organophosphate and pyrethroid pesticides and behavioral problems in Canadian children. Environ Health Perspect. 2013;121(11-12):1378-1384. doi:10.1289/ehp.1306667. DACO 4.8
3613519	Hossain MM, DiCicco-Bloom E, Richardson JR. Hippocampal ER stress and learning deficits following repeated pyrethroid exposure. Toxicol Sci. 2015;143(1):220-228. doi:10.1093/toxsci/kfu226. DACO 4.8
2967885	Ben Slima A, Chtourou Y, Barkallah M, Fetoui H, Boudawara T, Gdoura R. Endocrine disrupting potential and reproductive dysfunction in male mice exposed to deltamethrin. Hum Exp Toxicol. 2017;36(3):218-226. doi:10.1177/0960327116646617. DACO 4.8

PMRA Document Number	Reference
3613521	Ben Slima A, Ben Abdallah F, Keskes-Ammar L, Mallek Z, El Feki A, Gdoura R. Embryonic exposure to dimethoate and/or deltamethrin impairs sexual development and programs reproductive success in adult male offspring mice. Andrologia. 2012;44 Suppl 1:661-666. doi:10.1111/j.1439-0272.2011.01246.x. DACO 4.8
3613525	Galal MK, Khalaf AA, Ogaly HA, Ibrahim MA. Vitamin E attenuates neurotoxicity induced by deltamethrin in rats. BMC Complement Altern Med. 2014;14:458. Published 2014 Dec 2. doi:10.1186/1472-6882-14-458. DACO 4.8
3613526	Lu Q, Sun Y, Ares I, et al. Deltamethrin toxicity: A review of oxidative stress and metabolism. Environ Res. 2019;170:260-281. doi:10.1016/j.envres.2018.12.045. DACO 4.8
3613534	Viel JF, Warembourg C, Le Maner-Idrissi G, et al. Pyrethroid insecticide exposure and cognitive developmental disabilities in children: The PELAGIE mother-child cohort. Environ Int. 2015;82:69-75. doi:10.1016/j.envint.2015.05.009. DACO 4.8
3613535	Glorennec P, Serrano T, Fravallo M, et al. Determinants of children's exposure to pyrethroid insecticides in western France. Environ Int. 2017;104:76-82. doi:10.1016/j.envint.2017.04.007. DACO 4.8