Re-evaluation Note REV2018-17

Initiation of Cumulative Health Risk Assessment – N-Methyl Carbamates

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
hc.pmra.publications-arla.sc@canada.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
hc.pmra.info-arla.sc@canada.ca

Canada

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Initiation of Cumulative Health Risk Assessment – N-Methyl Carbamates

This notice is to advise that pursuant to subsection 16(1) of the *Pest Control Products Act*, Health Canada's Pest Management Regulatory Agency (PMRA) is initiating a re-evaluation related to pest control products containing active ingredients belonging to the N-methyl carbamate (NMC) class of pesticides. This will include the NMC pesticides that are registered in Canada, namely: carbaryl, formetanate hydrochloride, methomyl, oxamyl and propoxur. The re-evaluation will be focused on the assessment of the cumulative health effects of the NMCs as described in SPN2018-02, *Cumulative Health Risk Assessment Framework*.

The common mechanism of toxicity for the NMCs centres on their well-established ability to inhibit acetylcholinesterase by carbamylation of the serine hydroxyl group located in the active site of the enzyme. This mechanism of action results in cholinergic toxicity that manifests quickly after exposure, followed by rapid recovery.

Table 1 lists the five NMCs registered in Canada and the anticipated exposure scenarios resulting from the uses for each NMC. Additional pesticides that belong to the NMC common mechanism group include carbofuran, aldicarb, bendiocarb, methiocarb, pirimicarb and thiodicarb. Although not registered in Canada, these active ingredients could be present on imported food commodities and will also need to be considered. A scoping assessment/problem formulation is also included in Appendix I.

Appendix I Scoping Assessment/Problem Formulation for NMC Cumulative Risk Assessment

Scoping Assessment/Problem Formulation

a. Background

The purpose of the scoping assessment is to identify the available information relating to evidence of a common mechanism of toxicity, use pattern, and likelihood of co-exposure to the pesticides being considered. The information collected at this stage allows the PMRA to determine whether a cumulative risk assessment is required, and if so, to identify the scope and depth of the necessary analysis. Data types and information sources are also identified at this step.

As part of the approach to cumulative risk assessment, SPN2018-02 indicates that the PMRA will leverage cumulative assessments undertaken by other regulators, provided that the assessments are relevant to the Canadian context. The United States Environmental Protection Agency (USEPA) has established the NMCs as a common mechanism group based on the shared structural characteristics and common mechanism of toxicity. Following an assessment of the USEPA NMC revised cumulative risk assessment (2007),[1] the PMRA has determined that there is scientific validity in establishing the NMCs as a common mechanism group. Given that the risks associated with the individual NMCs have now been adequately characterized by way of a modern assessment and mitigated to acceptable levels, it is appropriate to proceed with a cumulative risk assessment.

b. NMC Pesticides, Uses and Pathways

NMCs are generally used for insect control. Five NMC active ingredients are currently registered in Canada: carbaryl, formetanate hydrochloride, methomyl, oxamyl and propoxur. Table 1 lists these five NMCs and the anticipated exposure scenarios resulting from the uses for each NMC. Additional pesticides that belong to the NMC common mechanism group include carbofuran, aldicarb, bendiocarb, methiocarb, pirimicarb and thiodicarb. Although not registered in Canada, these active ingredients could be present on imported food commodities and accordingly, are included in the scoping assessment.

[1] United States Environmental Protection Agency (2007). Revised N-Methyl Carbamate Cumulative Risk Assessment. Washington, DC. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides Accessed 5 July 2018

Table 1: Summary Information for NMC Pesticide Uses and Exposure Pathways

Active Ingredients	PMRA Re-evaluation Documents*	Pesticide Uses	Potential Exposure Pathways		
			Food	Drinking Water	Residential
Carbaryl	PRVD2009-14 RVD2016-02	Fruit Trees	X	X	
		Agricultural Crops	X	X	
		Forests and Woodlands		X	X
		Farmland		X	
		Ornamentals		X	X
		Bran Bait			X
Formetanate hydrochloride	PRVD2008-26 RVD2009-05	Fruit Trees	X	X	
Methomyl	REV2009-02 REV2010-08 PRVD2016-02 RVD2018-05	Agricultural Crops	X	X	
		Granular bait[a]			
Oxamyl	PRVD2007-02 RVD2008-05	Fruit Trees		X	
		Agricultural Crops	X	X	
Propoxur	PRVD2011-09 RVD2014-01	Outdoor Structural		X	X
		Indoor Commercial[b]			
		Bait Trays			X
Note: The following NMC active ingredients are not registered in Canada, however, these active ingredients will need to be considered as they could be present on imported food commodities.					
Carbofuran	PRVD2009-11 RVD2010-16 (cancelled)	Foods Imported to Canada	X		
Aldicarb Bendiocarb[c] Methiocarb[c] Pirimicarb Thiodicarb	-	Foods Imported to Canada	X		

*PRVD: Proposed Re-evaluation Decision; RVD: Re-evaluation Decision

[a] Granular bait for methomyl is registered for use in farm buildings, kennels, and poultry houses. Residential, dietary, and drinking water exposures are not expected from these applications.

[b] Indoor commercial uses of propoxur are limited to non-residential settings (for example, warehouses); thus, residential exposure is not expected from this use.

[c] Methiocarb has no registered food uses, maximum residue limits (MRLs), or tolerances in Canada or the United States, however, methiocarb does have Codex MRLs for certain food commodities. Nonetheless, domestic consumption of these food commodities is primarily sourced from Canada, the United States, and Mexico, none of which have food use registrations. For bendiocarb, there are no registered food uses, Canadian MRLs, American tolerances, or Codex MRLs. As such, the potential for residues of methiocarb or bendiocarb in the Canadian food supply is negligible and they will be excluded from the cumulative risk assessment.

c. Toxicity Assessment

The common mechanism of toxicity for the NMCs centres on their well-established ability to inhibit acetylcholinesterase by carbamylation of the serine hydroxyl group located in the active site of the enzyme. This mechanism of action results in cholinergic toxicity that manifests quickly after exposure, followed by rapid recovery.

For the hazard analysis, the PMRA anticipates following the relative potency factor method used by the USEPA (2007). The use of relative potency factors will allow the PMRA to convert exposures of all the chemicals in the NMC group into exposure equivalents of an index chemical, selected from the NMC group.

Specifically, the PMRA anticipates using a direct measure of the mechanism of toxicity, namely, brain cholinesterase inhibition, for each individual NMC to establish relative potency factors. The USEPA (2007) has demonstrated that brain cholinesterase inhibition is more robust than blood measurements of cholinesterase inhibition. Consequently, they established brain cholinesterase as the relevant endpoint for cumulative assessment. The PMRA agrees with this conclusion, and will be following a similar approach. As new cholinesterase inhibition data have become available since the USEPA assessment, the PMRA will re-assess the relative potencies of the NMCs using benchmark analysis of the brain cholinesterase data for relevant routes of exposure. Data from relevant toxicity studies in adult and juvenile animals, measuring brain cholinesterase inhibition at peak inhibition following exposures, will be used for determining points of departure and for informing the *Pest Control Products Act* factor. Recovery data may also be used, depending on the level of refinement required.

d. Exposure Assessment – Food

The cumulative risk assessment for the NMC pesticides will examine exposures that may occur through the dietary pathway. This approach is similar to that used for the single chemical aggregate assessments, in that the cumulative risk assessment will evaluate residues on foods treated with pesticides belonging to the common mechanism group, as well as those which may occur in drinking water. Exposure through drinking water will only occur from the outdoor uses of NMCs registered in Canada. Residues on foods may occur as a result of the registered use in Canada, or through residues on foods imported into Canada. As such, the dietary exposure assessment will consider international as well as Canadian food use registrations.

The specific food/pesticide combinations that will be included in the cumulative risk assessment will be based on an analysis of Maximum Residue Limits (MRLs)/Tolerances and food use registrations (see Table 2), as well as food residue monitoring data. Certain NMC pesticides may be excluded from the cumulative risk assessment if it is determined their registrations are not relevant to the Canadian food supply. The data sources used to inform the assessment include the North American registration status for the pesticides, food residue monitoring data (Canadian Food Inspection Agency National Chemical Residue Monitoring Program; United States Department of Agriculture Pesticide Data Program), Canadian crop production information, and trade data.

Methiocarb has no registered food uses, MRLs, or tolerances in Canada or the United States, however, methiocarb does have Codex MRLS for certain food commodities. Nonetheless, domestic consumption of these food commodities is primarily sourced from Canada, the United States, and Mexico, none of which have food use registrations. For bendiocarb, there are no registered food uses, Canadian MRLs, American tolerances, or Codex MRLs. As such, the potential for residues of methiocarb or bendiocarb in the Canadian food supply is negligible and they will be excluded from the cumulative risk assessment.

Table 2: Summary of NMC food use pesticides

NMC Pesticide	Canadian Registered Food Use	Canadian MRL	American Tolerance	Codex MRL
Carbaryl	Yes	Yes	Yes	Yes
Formetanate hydrochloride	Yes	Yes	Yes	
Methomyl	Yes	Yes	Yes	Yes
Oxamyl	Yes	Yes	Yes	Yes
Carbofuran		Yes	Yes	Yes
Aldicarb		Yes	Yes	
Methiocarb				Yes
Pirimicarb		Yes		Yes
Thiodicarb			Yes	Yes
Bendiocarb				

e. Exposure Assessment – Drinking water

Exposure from drinking water will be assessed through modeling and available relevant water monitoring information.

Modeling for the NMC pesticides registered in Canada was conducted previously as part of the individual re-evaluations. For some of the active ingredients in this group, it may be necessary to update the water modeling. This includes updating the fate inputs as well as the models used. Those NMCs that are not registered in Canada, but potentially present on imported food only, will not need to be considered in the cumulative risk assessment as a contributor to drinking water exposure.

f. Exposure Assessment – Residential

The only NMC pesticide that retains registrations for domestic-class products is propoxur (that is, bait trays and outdoor structural uses). Based on the USEPA Residential Standard Operating Procedures, residential exposure from use of bait trays was considered to be negligible because the active ingredient is enclosed in a self-contained unit and is not available for exposure. Postapplication exposure from outdoor structural applications of propoxur were also considered to be negligible, provided that these outdoor applications are not made to vegetation, plants, grass or any area accessible to children. However, residential applicators have the potential for dermal and inhalation exposure when applying outdoor structural products. These routes of exposure could potentially co-occur with the dietary and drinking water exposures and would need to be considered in the cumulative risk assessment. The USEPA Residential Standard Operating Procedures will be used to assess residential exposure for the cumulative risk assessment.

Carbaryl has some uses that could potentially result in bystander residential exposure (for example, forest, woodlands, rights-of-way, ditch banks, and field borders). Bystanders in these scenarios have the potential for dermal exposure, which could also co-occur with dietary and drinking water exposures and would need to be considered in the cumulative risk assessment. The USEPA Residential Standard Operating Procedures and the Agriculture Re-entry Exposure Task Force database will be used to determine bystander residential exposure. Bystander exposure to carbaryl from bran bait applications is not expected, based on the formulation type.

g. Conclusion

Given that a common mechanism of toxicity and potential for co-exposure to the pesticide being considered have been identified for NMC pesticides, a cumulative risk assessment is required. The common assessment group that will be considered in the cumulative risk assessment will include carbaryl, formetenate hydrochloride, methomyl, oxamyl, propoxur, carbofuran, aldicarb, pirimicarb and thiodicarb. Bendiocarb and methiocarb are excluded from further consideration in light of their use pattern and anticipated negligible exposure, as explained above. The oral (all chemicals in the common assessment group except propoxur), dermal (propoxur and carbaryl) and inhalation (propoxur) routes will be considered for co-exposure.

Data Gathering

The PMRA will make use of available information, including registrant-supplied data, foreign reviews as well as relevant data from the open scientific literature. An Announcement of Data Call-In outlining the information required from registrants will be placed in the Public Registry.

Although some NMCs are not registered in Canada, they may contribute to cumulative risk through residues on imported commodities. Registrants are encouraged to submit any relevant data related to global use patterns to inform the extent that these NMCs may contribute to the cumulative risk assessment. Toxicology data in the open scientific literature will be used to the extent possible; however the PMRA also encourages the submission of relevant toxicity data (specific to dose-response and/or recovery for cholinesterase inhibition following acute oral gavage exposure), if available.

Next Steps

Following examination of the extent of available data and information, Health Canada will publish a work plan for the cumulative risk assessment and initiate the full review. The work plan will include target dates for the publication of the proposed cumulative health risk assessment for consultation, as well as for the final assessment.