

Review Panel Report to
Health Canada Pest Management Regulatory Agency
Re: Notice of Objection for RVD2021-05
Re-evaluation Decision: Imidacloprid and Its Associated End-use Products: Final Decision

Chair:

Dr. David Dall

Australian Pesticides and Veterinary Medicines Authority, Canberra, Australia

Panel Members:

Professor and Jarislowsky Chair in Environment and Health Dr. Karen Kidd

Department of Biology, McMaster University, Ontario, Canada

Associate Professor Dr. Ryan Prosser

School of Environmental Sciences, University of Guelph, Ontario, Canada

February 2026

Executive Summary

Following finalisation of the re-evaluation decision of imidacloprid by PMRA in 2021 (RVD2021-05) a Notice of Objection was received by Health Canada regarding the methodology used to derive an effects metric for chronic exposure of freshwater aquatic invertebrate communities, and the quantitative value adopted. In response Health Canada established a panel of independent scientists which was requested to provide opinion on whether the adopted subject metric is sufficiently protective of aquatic invertebrate communities.

The Panel examined documentation provided by PMRA, which included a detailed report of an outdoor microcosm study from which the metric was derived, as well as a range of scientific and technical literature in the public domain.

The Panel concluded that microcosm-based assessment is an acceptable methodology for establishing the relevant metric, that the focal species used in the key microcosm study was appropriate for the purpose, and that the microcosm study was of sufficient reliability to be suitable for use. The Panel also noted that allowance was made by PMRA for dissipation of imidacloprid over the course of the study in deriving the adopted time-weighted average (TWA) 28-day No Observed Effect Concentration (NOEC) metric of 0.16 µg imidacloprid/L.

On the basis of these and other considerations provided below the Panel is of the opinion that the adopted chronic aquatic effects metric (NOEC of 0.16 µg a.i. time weighted average (TWA)/L) is appropriate for use, and is sufficiently protective of aquatic invertebrate communities.

1. Background information

Imidacloprid is a member of the neonicotinoid class of insecticides. It is widely used in agricultural settings including as foliar sprays, soil drenches and seed treatments, and also has a range of veterinary and domestic applications. Imidacloprid has high levels of activity against insects and some other arthropods, and thus may also pose unintended risks to non-target species in both terrestrial and aquatic environments.

Consistent with Health Canada's policy of cyclical re-evaluation of registered pesticides by its Pest Management Regulatory Agency (PMRA), a 'Proposed Re-evaluation Decision: Imidacloprid' (PRVD2016-20) was released in 2016; after public consultation and revision the 'Re-evaluation Decision: Imidacloprid and its Associated End-use Products – Final Decision' (RVD2021-05; 'Final Decision') was released in 2021.

During the process of finalisation from PRVD2016-20 to RVD2021-05 some revisions were made to assessment processes and resultant contents of the document, including to the method of assessment and quantitation of the chronic effects metric for freshwater invertebrate organisms. The revision to this effects metric was based on data from a newly available higher tier microcosm study of the effects of imidacloprid on larval survival and adult emergence of a summer cohort of the mayfly *Cloeon dipterum* ('Outdoor microcosm study to the effects of IMIDACLOPRID SL 200 on the summer generation of the mayfly *Cloeon dipterum*', 2015; PMRA #2744281). From this study a deterministic No Observed Effect Concentration (NOEC) endpoint of 0.16 µg active ingredient (a.i.)/L 28-day time weighted average (TWA) was adopted, derived from the nominal treatment level of 0.243 µg a.i./L.

The deterministic metric was adopted in preference to a more recently calculated probabilistic hazard concentration for 5% of species (HC₅) metric of 0.011 µg a.i./L derived from a species sensitivity distribution (SSD) of low effect endpoints from laboratory toxicity tests with 14 freshwater invertebrate species. The lowest endpoint data in that SSD were the EC₁₀ (immobilisation) values for

larvae of the Ephemeroptera species *Cloeon dipterum* and *Caenis horaria* of 0.033 and 0.024 µg a.i./L, respectively, from Roessink et al (2013). This HC₅ metric itself replaced a previously proposed SSD-derived HC₅ of 0.041 µg a.i./L based on LC₅₀ values for 10 freshwater species.

Following release of the Final Decision, a Notice of Objection was received by Health Canada suggesting, *inter alia*, that if a microcosm-derived effects metric was to be adopted, an uncertainty factor (suggested to be in the range of 2-10) should be applied to the determinative endpoint in order to make allowance for the lack of precision inherent in such studies.

PMRA has acknowledged that it is current practice for the PMRA to apply an uncertainty factor of one (1) to NOECs, and that it did not consider application of a larger uncertainty factor to the microcosm-derived NOEC endpoint of 0.16 µg a.i./L, despite possible limitations on its statistical reliability being suggested by the accompanying estimate of the minimum detectable difference (MDD) parameter.

In view of this situation, PMRA concluded that this aspect of the objection raised scientifically founded doubt as to the validity of this evaluation on which a decision was based, and therefore that it should be referred to a review panel for further consideration and advice consistent with subsection 35(3) of the *Pest Control Products Act* (S.C. 2002, c.28).

2. Request to the Panel

The Panel was requested to provide advice and recommendations to the Minister with respect to the following questions:

1. Is the effects metric (NOEC of 0.16 µg a.i. time weighted average (TWA)/L, equivalent to 0.243 µg/L nominal, from the 2015 study, “Outdoor microcosm study to the effects of IMIDACLOPRID SL 200 on the summer generation of the mayfly *Cloeon dipterum*.” (PMRA #2744281) sufficiently protective of aquatic invertebrate communities?
2. If not, how would you recommend the PMRA approach the effects metric selection from the identified microcosm studies?

3. Review Process

The PMRA provided publicly available and confidential materials including the documents ‘Proposed Revaluation Decision: Imidacloprid’ (PRVD2016-20), ‘Re-evaluation Decision, Imidacloprid and Its Associated End-use Products, Final Decision (RVD2021-05) and the microcosm study referenced above (PMRA #2744281). The Panel reviewed these materials, the Notice of Objection, the received submission to the panel review, and other supporting information identified below.

Panel observations on PRVD2016-20 and RVD2021-05

The Panel reviewed relevant content of PRVD2016-20 and RVD2021-05 and noted some inaccuracies in text provided in RVD2021-05 Section 3.3.3.1.2 ‘Chronic toxicity effects metrics’ (pg 36).

Content in that section included the statement:

‘The endpoint for the most sensitive species reported in PRVD2016-20 was a 28-d EC₁₀ of 0.024 µg a.i./L for *Cloeon dipterum* based on significant reductions in emergence (Roessink et al, 2013; PMRA #2544385). This endpoint remains the most sensitive chronic endpoint for aquatic invertebrates.’

The panel suggests that the lowest endpoint for *Cloeon dipterum* reported in PRVD2016-20 was a 28d EC₅₀ of 0.00012 mg/L (Appendix IX, pg 175) which was based on larval immobilisation observations reported in Roessink et al (2013). In contrast, the quoted endpoint of 0.024 µg a.i./L relates to a 28-d

EC₁₀ for the ephemeropteran *Caenis horaria*, also based on larval immobilisation. For the 28-d EC₁₀ immobilisation metric, the reported value for *C. dipterum* is 0.033 µg a.i./L (Roessink et al, 2013).

While these inconsistencies do not directly affect interpretation of the relevant microcosm study, the panel notes that the identified statement relating to species sensitivity and the endpoint value and character cannot be accepted as provided.

Nevertheless, the panel also notes that, on the basis of other metrics (e.g. 28-d LC₁₀ and 28-d EC₅₀ immobilisation), *Cloeon dipterum* can be identified as the most sensitive freshwater invertebrate species for which information is available from imidacloprid exposures.

Panel observations on PMRA #2744281 ‘Outdoor microcosm study to the effects of IMIDACLOPRID SL 200 on the summer generation of the mayfly Cloeon dipterum’ (June 2015)

The Panel reviewed the test design of the referenced outdoor microcosm study from the perspective of alignment with best practice recommendations that support statistical analyses of results, including estimation of the MDD parameter.

The Panel noted that the test design was consistent with general recommendations to use five or more test substance treatment concentrations, at least two replicate test systems per treatment, and preferably a larger number of replicate test systems as experimental controls (see e.g., Brock et al, 2015). It also provided raw data, pre-treatment assessment of measurement endpoints, and sufficient analytical data to characterize the dissipation of imidacloprid in the test systems, these being criteria that PMRA considers critical for the use of toxicity data from higher tier studies (including microcosm and mesocosm experiments) in quantitative risk assessments of pesticides.

The Panel observed that the study was undertaken in the period 4 July to 4 September 2014, and focussed on the highly imidacloprid-sensitive summer cohort of the ephemeropteran *Cloeon dipterum*; on the basis of laboratory studies noted above, this species is considered to be among the most sensitive freshwater invertebrate species for which information is available.

Experimental data and statistical treatments provided in the report were reconsidered by PMRA on the basis of assessed non-normality of data distribution, and the adopted NOEC of 0.16 µg TWA/L was calculated from the nominal concentration of 0.243 µg/L. The Panel was provided limited detail of the statistical re-analysis by PMRA, and thus does not provide comment on this aspect. The Panel noted that the MDDs of 51 and 59 provided in the report for days 23 and 30, respectively, are within a range at which medium-sized effects are considered to be statistically detectable (EFSA 2013; ‘Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters’).

Panel observations on PMRA #2744280 ‘Outdoor microcosm study to the effects of IMIDACLOPRID SL 200 on the mayfly Cloeon dipterum and its dissipation from water at two different light intensities’ (February 2014)

The outdoor microcosm study PMRA #2744280 was undertaken in the period 2 October to 13 November 2013 on the same site, with the same focal species (i.e., *Cloeon dipterum*), using a largely identical study design to that of study PMRA #274481 (see above). Consistent with the Panel’s review of PMRA #274481, the panel noted acceptability of design, procedures and reporting protocols associated with this study.

A key difference between the two studies was that this study (#2744280) was done under Fall (Autumn) environmental conditions, whereas #2744281 was done under Summer conditions. Microcosm variables such as water temperature and light intensity reflected the difference in

seasonality, with, for example, morning water temperatures ranging from 5.5° to 14.8°C in this study (#2744280) compared to 15.6° to 23.7°C in the Summer study (#2744281).

The most significant difference between the two, however, was that study #2744280 found no adverse effect of imidacloprid on the focal species, including at the nominal maximum tested concentration of 3.8 µg/L.

The Panel noted that the MDDs of 57% and 63% reported for days 23 and 30, respectively, for #2744280 are within a range at which medium-sized effects are considered to be statistically detectable (Brock et al, 2015). The European Food Safety Authority's Panel on Plant Protection Products and their Residues recommended that the MDD be reported for each endpoint measured in a micro-/mesocosm study, but also that the MDD fall within Class II or greater (EFSA, 2013). Classes II, III, and IV represent MDDs of 70-90%, 50-70%, and <50%, respectively (EFSA, 2013). The MDDs reported in #2744280 both fall within Class III, thus aligning with the recommendation (EFSA, 2013). The Panel also noted the relative correspondence of MDDs between the two studies at these time points, which, in addition to individually informing of the potential for detectability of effects, may also be considered broadly indicative of reproducibility of experimental performances under the study design that was used.

Comparison of microcosm and laboratory study results

The differences observed in sensitivity of *Cloeon dipterum* to imidacloprid in microcosm studies done under different seasonal conditions are broadly aligned with laboratory studies on the same combination of test species and chemical. Thus, laboratory studies of this species and imidacloprid provided estimates for a chronic exposure (28 day) EC₅₀ of 0.13 µg/L (CI: 0.070 – 0.23) for a summer (August/September) cohort, and 0.68 µg/L (0.45-1.00) for a fall/winter cohort (Roessink et al, 2013; Van den Brink et al, 2016).

The same laboratory studies also reported parallel seasonal differences in acute (96 hr) EC₅₀ sensitivities for several species of aquatic arthropods, including *Cloeon dipterum* and *Caenis horaria*.

Review of the adopted chronic aquatic endpoint

After review of the relevant materials as outlined above, the Panel applied a structured 'decision tree' approach to consider the chronic aquatic endpoint adopted in RVD2021-05. This process involved sequential consideration of three key questions:

1. Does the panel consider adoption of a microcosm-derived determinative endpoint to be an acceptable basis for assessment?

The Panel notes that data from higher tier studies such as freshwater microcosm assessments are widely considered to provide more realistic assessments of the effects of chemical pesticides than data derived only from laboratory-based studies (Lahr et al, 2022). This conclusion is based on considerations that outcomes of higher tier studies implicitly incorporate the effects of environmental factors such as temperature and light intensity variation, potential geochemical effects from the presence of sediments, and biological effects from the presence of multi-trophic ecological cohabitants. Consistent with the broad scientific consensus, the Panel considers that adoption of a microcosm-derived determinative endpoint is – in principle – an acceptable basis for assessment of pesticide toxicity.

That said, it is acknowledged that experimental design and realised practical quality are important elements in assessment of the reliability for use of the results of any higher tier study. In the context under consideration, the Panel notes that two essentially replicate higher tier studies (provided as PMRA #2744281 and PMRA #2744280; see Section 3 for reviews) of potentially informative value are available. Both studies meet general experimental design recommendations (Brock et al, 2015),

and show similar robustness of observational data as assessed by their reported MDD parameters. In both instances reported MDDs for Days 23 and 30 suggest that pesticide-mediated effects of medium size would be detectable at those times.

On the basis of both the general and specific considerations outlined above, the Panel considers, firstly, that adoption of a microcosm-derived determinative endpoint is an acceptable in-principle basis for assessment, and secondly, that the study from which the value under consideration was derived (PMRA #2744281) is of sufficient overall reliability as to support its use for this purpose.

2. Does the panel consider the adopted indicator taxon (*Cloeon dipterum*), and assessed seasonal form and life stage(s) to be acceptable bases for assessment?

On the basis of compiled faunal abundance endpoints (e.g., 28-d TWA) from multiple freshwater mesocosm studies with imidacloprid (see e.g. 'PMRA – Environmental Assessment Directorate Monograph – Re-evaluation of imidacloprid – Appendix VI Imidacloprid Mesocosm Effect Assessment', PMRA #3211597, Table 3), it can be accepted that Ephemeroptera (mayflies) are at least among the most sensitive freshwater taxa, and potentially represent the most sensitive taxon with regard to chronic exposures. This conclusion is supported by reported laboratory tests on a smaller number of aquatic insect and microcrustacean taxa, among which larvae of the representative mayfly taxa *Cloeon dipterum* and *Caenis horaria* showed substantially higher acute and chronic sensitivities than other insect and crustacean taxa (Roessink et al, 2013; Van den Brink et al, 2016). *C. dipterum* larvae were concluded to be the most sensitive tested species with respect to chronic imidacloprid exposure (Roessink et al, 2013).

As reviewed above, evidence from laboratory and microcosm studies has also identified seasonal differences in susceptibility to imidacloprid in multiple aquatic taxa, with summer cohorts, including those of *C. dipterum*, generally being more sensitive than overwintering cohorts.

Consideration of this body of evidence leads the Panel to conclude that use of sensitivity data for chronic exposure of summer cohort larvae of *Cloeon dipterum* to imidacloprid provides a relevant and acceptable basis for setting a chronic aquatic exposure endpoint.

3. Is the chronic aquatic toxicity effect metric adopted in RVD2021-05 (i.e., a NOEC of 0.16 µg TWA/L; 0.243 µg/L nominal) an acceptable assessment outcome?

The Panel considered data provided in PMRA #2744281, including estimates of the relevant MDD parameter (see above), and concluded that the nominal treatment level of 0.243 µg/L showed a clear differentiation of total abundance of *C. dipterum* at days 23 and 30 as compared to the next highest treatment level (0.608 µg/L; Appendix 19). From this the Panel concluded that the nominal concentration of 0.243 µg/L provided an acceptable quantitation of the NOEC.

The Panel noted that study data were statistically re-analysed by PMRA, but does not provide comment on that analysis. The Panel also noted that allowance was made by PMRA (PMRA #3211597) for prospective dissipation of imidacloprid over the course of the study, such that the 28-d NOEC was adjusted to a TWA exposure of 0.16 µg/L.

On the basis of these considerations, the Panel concluded that the adopted 28-day NOEC of 0.16 µg TWA/L for *C. dipterum* is an acceptable assessment outcome of the referenced study. Noting that various laboratory and micro/mesocosm data indicate that larvae of *C. dipterum* are at least among the most sensitive taxa, the Panel further considered that it is acceptable to use the 28-day NOEC of 0.16 µg TWA/L with an assessment factor of one (1) as an endpoint for permissible aquatic community exposure.

4. Comments and conclusion

The adopted NOEC for the summer cohort of *Cloeon dipterum* is a direct outcome of appropriately refined data from the referenced microcosm study, but is also qualitatively and quantitatively consistent with independent data from laboratory studies and a parallel microcosm study with an overwintering cohort of *C. dipterum*. Taken as a whole, the body of data is considered to provide a reliable and relevant basis on which to determine a chronic effects metric which is sufficiently protective of aquatic invertebrate communities.

When reviewing data provided in the referenced microcosm study report (PMRA # 2744281) the Panel queried inclusion of counts of emergent adult *C. dipterum* made five days before commencement of exposure to the test chemical (see Appendix 16). The Panel noted that these counts provided a measure of confidence that test arenas had been appropriately established, but queried their relevance to subsequent experimental results. Nevertheless, informal examination of data excluding the Day(-5) counts from combined adult/larval abundance did not affect the conclusions drawn from the study.

5. Recommendation

The Panel was requested to consider two questions, the first being whether the aquatic effects metric adopted in RVD2021-05 (NOEC of 0.16 µg a.i. TWA/L), based on an outdoor microcosm study (PMRA #2744281), is sufficiently protective of aquatic invertebrate communities.

On the basis of considerations provided above, the Panel is of the opinion that the adopted aquatic effects metric is appropriate for use, and is sufficiently protective of aquatic invertebrate communities. It is recommended that the NOEC of 0.16 µg a.i. TWA/L be retained.

Having made this recommendation, the second question is not required to be addressed by the Panel.

6. Other Suggestions

The Panel observes that PMRA's ability to make robust regulatory decisions is heavily dependent on availability of rigorous studies that include relevant, reliable and complete reporting of study methods and results. It noted that several mesocosm studies were not included in the final assessment decision, sometimes because their design did not meet the minimum quality requirements for inclusion.

While recognizing that PMRA does not fund research, moving forward the Panel recommends that the Agency promote guidance materials and frameworks that can help to ensure experimental designs for both standard and non-standard studies, and the quality of reporting, are appropriate for use in review processes, and that increase the availability of all (eco)toxicology data for regulatory decision-making.

The OECD recently published the 'Guidance Document on the Generation, Reporting and Use of Research Data for Regulatory Assessments' (OECD, 2025). This document describes good practices for laboratory and higher tier (mesocosm) studies that can increase the inclusion of research data in regulatory contexts, as well as recommendations to various stakeholder groups. In addition, Lahr et al (2022) have published a 'Critical Appraisal Tool' methodology that specifically supports the evaluation of non-standard higher tier ecotoxicology studies for reliability and relevance. We encourage PMRA to examine and potentially promote their criteria and scoring system to improve the generation of data for regulatory assessments.

Finally, the Panel suggests that PMRA publicly communicate the rationale underlying adoption of protection at the community level as an appropriate regulatory setting for aquatic invertebrates.

References

Brock et al, 2015. The minimum detectable difference (MDD) and the interpretation of treatment-related effects of pesticides in experimental ecosystems. *Environmental Science and Pollution Research* 22, 1160-1174.

Lahr et al, 2022. Proposal for critical appraisal tools for the evaluation of ecotoxicology studies. Annex D. EFSA supporting publication 2022:EN-7787. 67 pp. doi:10.2903/sp.efsa.2022.EN-7787.

OECD, 2025. OECD Guidance Document on the Generation, Reporting and Use of Research Data for Regulatory Assessments. OECD Series on Testing and Assessment, No. 417, OECD Publishing, Paris, <https://doi.org/10.1787/8d49ec1d-en>.

Roessink et al, 2013. The neonicotinoid imidacloprid shows high chronic toxicity to mayfly nymphs. *Environmental Toxicology and Chemistry* 32, 1096-1100. (PMRA #2544385).

Van den Brink et al, 2016. Acute and chronic toxicity of neonicotinoids to nymphs of a mayfly species and some notes on seasonal differences. *Environmental Toxicology and Chemistry* 35, 128-133.