DEPARTMENT OF HEALTH

Protecting, Maintaining and Improving the Health of All Minnesotans

March 31, 2023

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Regulatory Scientific Affairs
Bayer U.S. LLC Crop Science Division
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Re: Proposed Amendments to Rules Governing Health Risk Limits for Groundwater, Minnesota Rules, Chapter 4717, Part 7500, Part 7850, and Part 7860; Revisor's ID Number RD4587, OAH Docket No. 5-9000-38941

Dear William Reeves:

Thank you for your comments on the proposed Health Risk Limit for imidacloprid during the Health Risk Limits Rules Amendment pre-hearing comment period. MDH's responses are below the points in the letter (numbered and *in italics*).

1. Minnesota's regulations for establishing health standards (Minnesota statues (sic) 144.0751[1]) require that when establishing drinking water quality standards, the Commissioner of Health must base those standards on scientifically acceptable, peer-reviewed information. Furthermore, Minnesota's regulations for establishing health risk limits (Minnesota statutes 103H.201[2]) require that "the adopted health risk limits shall be derived using United States Environmental Protection Agency (EPA) risk assessment methods using a reference dose, a drinking water equivalent, and a relative source contribution factor."

MDH used EPA methods to develop imidacloprid guidance as spelled out in statute[1,2]: we applied a reference dose, a drinking water equivalent, and a relative source contribution factor to develop guidance based on immunotoxicity data from a scientifically acceptable, peer-reviewed study in mice (Badgujar 2013)[3]. In addition, our Statement of Need and Reasonableness (SONAR)[4] states, "Risk assessment methods require that MDH determine the health effects associated with a chemical and the lowest dose at which an adverse effect may arise…" MDH selected an adverse effect (reduced delayed-type hypersensitivity) that occurs at a lower dose than the adverse effect chosen by EPA (tremors in dogs from a different study). Consequently, MDH's reference dose is lower than that derived by EPA. MDH is not obligated to use EPA's critical study, adverse critical effect, or reference dose. MDH has its own risk assessors that assess data and come to their own conclusions. The purpose of risk assessment is different between EPA and MDH. EPA's role is to

register pesticides, MDH's role is to derive water guidance that is protective, including a margin of safety, for sensitive and highly exposed individuals in the general population.[1,4]

2. Minnesota's proposed standard for imidacloprid does not meet any of these requirements because the underlying study Minnesota relied on (Badgujar et al., 2013[3]) is missing key information that would allow it to inform a quantitative risk assessment. Badgujar et al. (2013) does not provide sufficient information for reviewers to understand the details of the experiments they conducted, nor does it provide sufficient detail to determine whether the authors' observations were the result of confounding factors that were unrelated to imidacloprid.

MDH disagrees with Bayer Crop Sciences that Badgujar 2013, the 28-day immunotoxicity study in mice, does not meet the requirements to be a critical study used for risk assessment. Badgujar 2013 was published in an acceptable peer-reviewed journal, Environmental Toxicology and Pharmacology, published by Elsevier – an academic publishing company. MDH determined that the data in Badgujar 2013 clearly showed an immunotoxic effect that had a suitable dose-response alongside the correct controls. MDH was able to conduct a proper quantitative risk assessment with the data and information provided in the study. This satisfies Minnesota Statute 144.0751.

3. In two separate evaluations, the EPA has specifically considered Badgujar et al. (2013) and rejected it for use in quantitative risk assessments. EPA considered Badgujar et al. (2013) in its 2015 weight of evidence analysis of imidacloprid's ability to interact with the endocrine system[5] and its 2017 imidacloprid risk assessment for terrestrial organisms[6]. In both cases, EPA concluded that Badgujar et al. (2013) was not sufficient quality to inform a quantitative risk assessment. EPA's stated reasons included a lack of information about the imidacloprid sample used in the study, the absence of raw data to confirm the findings and statistical analysis, and limited information about test conditions.

It is unusual in the open literature for academic peer-reviewed studies to include raw data, and minute study details, due to journal article space and word number constraints. Studies are peer-reviewed to help ensure that study findings and conclusions are scientifically acceptable. As stated above, MDH was able to conduct a proper quantitative risk assessment in accordance with our statutes and within the framework described in our SONAR[1,2,4].

4. Badgujar et al. (2013) purports to demonstrate that imidacloprid caused toxicity to the immune system of female mice that were administered imidacloprid for 28 days. EPA requires specific tests to understand the potential of pesticides to harm immune function[7]. These tests follow internationally- accepted guidelines and must be conducted according to Good Laboratory Practice (GLP) Regulations[8]. These two requirements ensure that the studies are of sufficient quality to inform a quantitative risk assessment and that reviewers can understand whether the conclusions accurately reflect the data.

While it is true that industry uses GLP[8] and follows EPA's Immunotoxicity Guidelines (EPA 1998)[7], academia in the open literature uses peer-review and journal editors to assess the quality of their work. Badgujar 2013 went through a peer-review process and was deemed acceptable to publish in Environmental Toxicology and Pharmacology. This satisfies Minnesota Statute 144.0751.

5. An immunotoxicity study that followed EPA's required methods and GLP regulations is available for imidacloprid (Kennel, 2010)[9]. The maximum dose in this study was 186 mg imidacloprid/kg body weight/day, 18.6 times higher than the maximum dose that Badgujar et al. (2013) tested. Additionally, Kennel (2010) conducted the study using male rats, in accordance with EPA's guidelines for an immunotoxicity study[7] based on evidence that males are more sensitive than females and rats are more sensitive than mice. Badgujar et al. (2013) tested female mice only. EPA relies on Kennel (2010) in its human health and ecological risk assessments and has concluded that imidacloprid did not cause immunotoxicity at any of the tested doses.

EPA's guidelines on immunotoxicity testing do not consider every facet of the immune system, and EPA states "the tests in this guideline do not represent a comprehensive assessment of immune function"[7]. This document also stipulates that both rats and mice are acceptable test subjects for immunotoxicity and that either sex may be used in these studies. Therefore, it is acceptable that the Badgujar study tested immune function in female mice. It is possible that female mice are the most sensitive species, and that delayed-type hypersensitivity is particularly sensitive to imidacloprid's effects. More recently, (Shi 2020)[10] published a peer-reviewed immunotoxicity study where female mice had a less effective response in activating the innate immune response after imidacloprid exposure, providing more weight-of-evidence that imidacloprid does affect different facets of the immune system.

Although Bayer suggests that Kennel is the only acceptable immunotoxicity study for determining the immune effects of imidacloprid exposure, Kennel also has its limitations. Kennel only tested one functional attribute of the immune system – immunoglobin M (IgM) titers in the serum after antigen challenge. In addition, the control group of rats had extremely high standard deviations for their IgM titers, making it difficult to detect any immune differences between the control and treated groups. There was no mention in Kennel as to why the control group animals demonstrated such extreme variability in their immune response. This type of control animal response raises questions about experimental precision and methodology. Lastly, MDH observed that there was evidence of a reduction in IgM after imidacloprid treatment in treated animals, but because of the study limitations, statistical significance was not achieved.

Badgujar tested delayed-type hypersensitivity – a T cell mediated response. Kennel tested IgM concentrations in the serum – an antibody response. Badgujar and Kennel tested different mechanisms of the immune system. It is therefore plausible that imidacloprid acts upon multiple arms of the immune system and that Kennel did not test for the most sensitive immune effect.

6. We support Minnesota's efforts to protect public health by adoption of health risk limits for chemicals that could be present in groundwater. We also believe those limits should rely on high quality studies that are of sufficient quality to inform quantitative risk assessments. Badgujar et al. (2013) does not meet that standard and this position is consistent with the views of expert risk assessors at EPA. EPA identified an appropriate, health protective value (Reference Dose, RfD) in its human health risk assessment of 0.08 mg/kg body weight/day that should be used to establish groundwater health risk limits for Minnesota.

MDH thanks Bayer for their interest in our risk assessment and resulting guidance values for imidacloprid. MDH's expert risk assessors disagree with Bayer Crop Sciences that Badgujar 2013 is not an appropriate critical study for determining health-based guidance and disagree that EPA's RfD is protective of human health. As stated previously in our comments, Badgujar 2013 is a peer-reviewed immunotoxicity study that has been published in an acceptable journal and fulfills Minnesota statute 144.0751. Badgujar used a sensitive species (female mice) to detect changes in a sensitive immunotoxicity endpoint (delayed-type hypersensitivity) that was not tested by Bayer Crop Sciences. The RfD that EPA chose for imidacloprid (tremors in dogs) is not adequately protective of human health. It is 22 times higher than MDH's RfD of 0.0036 mg/kg-d and does not protect for immune effects, sperm effects, and metabolic effects occurring in animals at the lower imidacloprid doses that Badgujar 2013 and others reported in the academic open literature. Furthermore, both the State of Wisconsin and The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) have stated that EPA's RfD for imidacloprid is not health protective.[11,12]

Therefore, in accordance with our obligation and authority under Minnesota Statutes 114.0751 and 103H.201, MDH maintains its proposed HRL for imidacloprid to "adequately protect the health of infants, children, and adults[1]."

Sincerely,

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References

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[2]Minnesota Statutes. (2022). Health Risk Limits. 103H.201. https://www.revisor.mn.gov/statutes/cite/103H.201

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[7]EPA. (1998). Health Effects Test Guidelines OPPTS 870.7800 Immunotoxicity. https://www.regulations.gov/document/EPA-HQ-OPPT-2009-0156-0049

[8]40 CFR Part 160. Good Laboratory Practice Standards. https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-160

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