ENDOCRINE SOCIETY
Hormone Science to Health

Michael S. Regan
Administrator
United States Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

August 28, 2024

Dear Administrator Regan,

The Endocrine Society appreciates the opportunity to comment on the Environmental Protection Agency's interim registration review decision on dimethoate. Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization dedicated to the understanding of hormone systems and the clinical care of patients with endocrine diseases and disorders. Our membership of nearly 18,000 includes researchers who are advancing our understanding of the effects of exposure to chemicals that interfere with hormone systems, also known as endocrine-disrupting chemicals (EDCs).

Organophosphate (OP) pesticides, including dimethoate, are known to have neurotoxic effects though endocrine and other modes of action. We are especially concerned about the noted effects of dimethoate on thyroid hormone in adults, with uncertain effects on the young. We are confident that these effects are not accurately captured through the developmental neurotoxicity (DNT) battery used by the Agency in the assessment of dimethoate, leading to a proposed inappropriate elimination of the 10X Safety Factor (SF) for dimethoate required by the Food Quality Protection Act (FQPA) to protect children. We also question the rationale for eliminating other safety factors based on the results provided by New Approach Methods (NAMs). **We urge the US Environmental Protection Agency (the Agency) to MAINTAIN the 10X FQPA and other Safety Factors established for the protection of infants and children for all pesticides in the organophosphate class.** We encourage EPA to consider phasing out OP pesticides given their neurotoxic effects and replace them with safer alternatives.

Our specific scientific concerns include:

1. Dimethoate was one of the few chemicals evaluated through Tier 1 of the EDSP that triggered a Tier 2 investigation. However, after petition by the registrant, this was waived and further testing for effects on young animals has not been reported. There is sufficient evidence to question whether dimethoate can interfere with the thyroid hormone system – a critical regulator of human growth and development leaving individuals impaired for life when the system is disrupted. To exclude thyroid disruption as an important risk of dimethoate exposure, it is critical that additional studies be performed in the context of a DNT as originally requested. Endpoints of thyroid disruption must include those in the neonatal brain. Moreover, current ToxCast data indicate that dimethoate – not omethoate – can inhibit the enzyme responsible for thyroid hormone synthesis – thyroid peroxidase.
2. By collectively eliminating safety factors originally applied to the dimethoate risk assessment, the Agency is implying that they are certain that infants and children are not uniquely sensitive to the toxic effects of dimethoate, that acetylcholine esterase (AChE) inhibition is the only path

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> to neurotoxicity, and that the in vitro tests within the DNT battery capture all molecular initiating events (MIEs) relevant to neurotoxicity; this is not a scientifically supportable claim.

While the Agency has devoted significant resources to respond to the National Academy's call for the development of non-animal-based toxicity testing[1] to improve human risk assessment, there is no science-based developmental neurotoxicity battery of NAMs that has been established to inform risk assessment[2]. Moreover, the Agency is proposing to use a single *in vitro* assay – AChE inhibition – in association with their PBPK model to eliminate the 10X safety factor that is presently required by law to protect infants and children.

We urge the Agency to instead consider the approach illustrated by the European **P**artnership for the **A**ssessment of **R**isks from **C**hemicals (PARC). This project in the European Union endeavors to improve testing methods to be included in risk assessment, including assessment of developmental neurotoxicity with the goal of identifying ways to support risk assessment using non-animal testing in a way that is more science-based[3]. Proposing that the 10X safety factor for children be eliminated before the Agency develops this kind of science-based analysis of new and existing *in vitro* assays is premature and not scientifically justified, and ultimately is likely to harm children, particularly those most likely to be exposed to these pesticides due to environmental injustices.

As we argued in our comments on the near-term strategy for the Endocrine Disruptors Screening Program, negative results from NAMs should not be used to invalidate positive results from animal or human studies, nor should they be used to downgrade a chemical's hazard assessment[4]. Rather, they should only be used to *identify* hazards uncharacterized by animal studies or hazard assessment. In this context, studies in humans and in animals strongly indicate that dimethoate – and other OP pesticides – exert developmental neurotoxic effects through mechanisms that are unrelated to AChE inhibition. The DNT battery should therefore only aim to improve health protection through initial hazard screening, and a negative result from a NAM test alone should not result in a conclusion about chemical safety.

The position of the Endocrine Society is not unique with regard to the inappropriate use of NAMs for regulatory purposes at this point in time. In fact, a 2023 publication in the journal Environment International, with authors from the US EPA and many other regulatory agencies around the world noted[5]:

> "Data produced by using NAMs on their own are currently not perceived by the regulatory community as sufficient to conclude on a broad spectrum of chemical safety-related endpoints for plant protection products, industrial chemicals, cosmetics or pharmaceuticals."

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[1] Abt, E., et al., Science and decisions: advancing risk assessment. Risk analysis : an official publication of the Society for Risk Analysis, 2010. 30(7): p. 1028-36.
[2] Bal-Price, A. and E. Fritsche, Editorial: Developmental neurotoxicity. Toxicol Appl Pharmacol, 2018. 354: p. 1-2.
[3] Tal, T., et al., New approach methods to assess developmental and adult neurotoxicity for regulatory use: a PARC work package 5 project. Front Toxicol, 2024. 6: p. 1359507.
[4] https://www.endocrine.org/-/media/endocrine/files/advocacy/society-letters/2024/february/es-response-to-edsp-near-term-strategy-22feb24.pdf
[5] Schmeisser, S., et al., New approach methodologies in human regulatory toxicology – Not if, but how and when! Environment International, 2023. 178: p. 108082.

These same authors also wrote (emphasis added):

> "Most NAMs provide a readout at the molecular, genomic, transcriptomic, proteomic or cellular level. As such, they can be indicators of downstream apical effects at the organism level, but they cannot show such effects directly unless properly validated. **To establish trust in their predictive reliability, additional proof** of qualitative (e.g. via AOP networks), quantitative (e.g. by quantitative AOPs (qAOPs) and quantitative in vitro to in vivo extrapolation, QIVIVE) and temporal coherence with apical outcomes observed in vivo **is required**."

Another report, published in 2022 in the journal Archives of Toxicology, with several US EPA authors notes that there are multiple criteria that should be established to demonstrate that a NAM has human biological relevance, when human data are available (as is the case for dimethoate)[6]. These include (emphasis added):

"For endpoints **where human data** or reference chemicals **are available**, **demonstrate concordance of the NAM with human responses** to build confidence in its human biological relevance.

"When applicable, evaluate the traditional animal test method(s) in either a quantitative or qualitative capacity, taking into account the human biological relevance. When comparisons are appropriate, **demonstrate that the NAM reflects human biological understanding as well as or better than the traditional animal test method**."

In conclusion, the Agency's proposed use of NAMs to eliminate the FQPA and other safety factors is unjustified and poses risks to children's health. We strongly urge the Agency to MAINTAIN the total of 100X safety factors originally applied and develop a science-based framework for the use of NAMs in risk assessment. Thank you for considering our comments, if we can be of further assistance please contact Joe Laakso, PhD, Director of Science Policy at jlaakso@endocrine.org.

Sincerely,

John Newell-Price, MD, PhD, FRCP

President, Endocrine Society

[6] van der Zalm, A.J., et al., *A framework for establishing scientific confidence in new approach methodologies.* Arch Toxicol, 2022. **96**(11): p. 2865-2879.