ENDOCRINE SOCIETY
Hormone Science to Health

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

July 16, 2024

Dear Administrator Regan,

The Endocrine Society appreciates the opportunity to comment on the Environmental Protection Agency's **Acephate: Second Revised Draft Human Health Risk Assessment (DRA) in Support of Registration Review**. 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 exposures to chemicals that interfere with hormone systems, also known as endocrine-disrupting chemicals (EDCs).

Organophosphate pesticides, including Acephate, are known to have neurotoxic effects though endocrine and other modes of action. We are confident that these effects are not accurately captured through the developmental neurotoxicity (DNT) battery used by the Agency in the assessment of Acephate, leading to a proposed inappropriate elimination of the 10X Safety Factor (SF) for Acephate required by the Food Quality Protection Act (FQPA) to protect children. **We urge the US Environmental Protection Agency (the Agency) to MAINTAIN the 10X FQPA Safety Factor established for the protection of infants and children for all pesticides in the organophosphate class. The 10X Safety Factor should be the minimum factor applied considering that the reliance on the *in vitro* acetylcholinesterase (AChE) inhibition assay should not be employed to inform risk associated with a developmental neurotoxicant.**

Our specific scientific concerns include:

1. The use of the *in vitro* developmental neurotoxicity (DNT) battery, including the AChE assay, to eliminate uncertainty in the Weight of Evidence (WOE) evaluation of Acephate is an inappropriate use of a New Approach Methodology (NAM) for several reasons, including that AChE inhibition is not the only molecular initiating event by which Acephate, or other organophosphates evaluated in the same way, could affect brain development.
2. By eliminating the 10X safety factor, the Agency is implying that there is no uncertainty around the sensitivity of the developing human brain to the toxic effects of Acephate in infants and children; this is not a scientifically supportable claim.

2055 L Street NW
Suite 600
Washington, DC
20036

T. 202.971.3636
F. 202.736.9705

endocrine.org

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 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 injustice.

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 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 Acephate – 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 in a NAMs 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."

These same authors also wrote (emphasis added):

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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.

> "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 Acephate)[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 safety factor is unjustified and poses risks to children's health. We strongly urge the Agency to MAINTAIN the 10X FQPA safety factor 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.