UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

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MEMORANDUM

SUBJECT: Guidance for Registration Review Data Requests for Oxon Degradates of Organophosphate Insecticides (OP).

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This document provides registration review guidance for identifying the data needed to assess risk from oxon degradates of organophosphate insecticides. This guidance incorporates input from the Environmental Fate and Effects Division's Fate Technical Team and has been reviewed by EFED's senior science advisors. The guidance is general and in all cases, study needs and justifications should be tailored to the individual problem formulations.

Oxons are compounds formed by oxidative desulfonation of OPs that have a phophothionate group (P=S). Oxidation can occur through photolysis, aerobic metabolism, chlorination, or other oxidative processes. In some cases, data have shown oxons to be substantially more toxic than their parent compounds, so they may be an important factor in determining the risk resulting from OP use.

Ecotoxicity and environmental fate studies available in the current datasets are often not sufficient to address uncertainties related to the oxons. Attached is a tiered set of conditions to be considered in deciding what data will be necessary to quantitatively assess risk from oxon formation and exposure. At each step, conclusions may indicate that further data requests are warranted. See Appendix A for suggested language to introduce the tiered requirements in a problem formulation section on anticipated data needs.

1) Can an oxon form?

Phosphothionate OPs, listed below, may form oxons and so need to be considered in this guidance. In some cases, the sulfoxide and/or sulfone transformation products of these OPs may form oxons as well.

Azinphos Methyl	Diazinon	Methyl Parathion
Bensulide	Dimethoate	Phorate*
Chlorethoxyfos	Disulfoton*	Phosmet
Chlorpyrifos	Malathion	Phostebupirim
Coumaphos	Methidathion	Terbufos*

* These OPs have sulfoxide and/or sulfone degradates that may also form oxons.

In the absence of evidence to the contrary, if oxon formation is possible based on the structure of the compound (the presence of P=S bond), the baseline assumption will be that oxons may be formed and will be degradates of toxicological concern and, thus, further data will be required. Lack of detection in available laboratory studies where oxons were target analytes or monitoring data should be considered, but is not necessarily sufficient evidence to rule out the possibility of oxon formation and the need for a refined risk assessment.

Additional lines of evidence that should be considered to support decision making on data requests:

- *Has the oxon been detected in air or water monitoring data?*
  - Given the generally short half-lives of oxons in natural waters and the limitations of monitoring data, monitoring detections, even if limited, are strong evidence of the potential for acute environmental exposure to oxons.
- *Has the oxon been targeted and detected in field or laboratory studies?*
  - Terrestrial field dissipation, field residue, field volatility, etc.
  - Hydrolysis, photolysis in soil, water, or air, aerobic metabolism in soil or water, etc.
  - Water treatment studies[1].
- *If there are no detections in field or laboratory studies, are the data robust?*
  - Have oxons been included in the analysis? Are the detection limits and analytical methods sufficient to have detected oxons? Are the sampling intervals appropriate for oxon detection? Have all relevant processes been considered?

[1] Kamel, A. et al., Oxidation of selected organophosphate pesticides during chlorination of simulated drinking water, Water Research (2008), doi:10.1016/j.watres.2008.10.038

2) If the oxon can form, then additional data are needed to determine if the oxon is of toxicological concern.

The oxon is a degradate of toxicological concern and will need to be considered in the risk assessment if its toxicity and the amount in which it is formed are sufficient to affect risk conclusions or risk mitigation strategies.

Both toxicity and environmental fate need to be considered in answering this question. In the set of criteria discussed below, toxicity is considered first. Although this is not typically the case, given the variety of potential routes of oxon formation, it is difficult to confirm based on fate studies alone that there is no concern. Additionally, toxicity studies are shorter term and so there will be less delay in the timeline for study submission.

2a) Toxicity

If the oxon can form, data are required to determine if the oxon is of sufficient toxicity to affect risk conclusions. If acceptable data are not available, studies should be requested. See Appendix A for suggested language to describe "How the data could impact the Agency's future decision making" in data justifications.

Data needed, using the *oxon* as the test substance:

- Acute Toxicity – Fish
- Acute Toxicity – Aquatic Invertebrates
- Acute Toxicity – Birds
- Acute Toxicity – Small Mammals. (Appropriate data may be available from HED)
- Other data may be needed on a case by case basis. For example, there are some cases in which chronic toxicity may be an issue, or there are cases where testing using the formulated product would be necessary.

2b) Environmental Fate

If the oxon can form and is toxic, data are required to determine the processes through which it may form and the extent of its formation. If acceptable data are not available, studies should be requested.

Data needed, using the *parent OP* as the test substance:

- Photolysis in Soil and Water
- Aerobic Metabolism in Soil or Water
- Lab and/or field volatility

- Photodegradation in air
- Water Chlorination
- Studies already available may be sufficient to provide these data, both from the submitted dataset and, for qualitative information about water chlorination, there is a study available from ORD/BEAD[1]. If studies of these processes are currently available, the robustness of the data in regards to oxon formation must be evaluated.

3) **If the oxon is a degradate of concern, then additional data are needed to quantify potential oxon exposure, persistence, and risk.**

Data needed, using the *oxon* as a test substance.

- Aerobic Soil Metabolism
- Batch Equilibrium
- In some cases, studies of the parent compound may be sufficient to provide these data. For example, if studies of the parent compound indicate that the oxon is a transient product, additional data on the oxon are not necessary.

[1] Kamel, A. et al., Oxidation of selected organophosphate pesticides during chlorination of simulated drinking water, Water Research (2008), doi:10.1016/j.watres.2008.10.038

APPENDIX A
Example language for oxon data justifications

Anticipatied Data Needs

The Agency expects to conduct a quantitative assessment of all degradates of toxicological concern in Registration Review. In the absence of data, the oxon degradate is presumed to be of greater toxicity than the parent, based on the toxicity profiles of similar organophosphate insecticides. The studies anticipated to be needed will provide data about the toxicity, formation, and fate of these oxons.

The need for oxon formation data is dependent on the results of the requested toxicity studies. That is, if oxon toxicity studies demonstrate that the oxons are not of sufficient toxicity to alter risk conclusions or to impact mitigation decisions, then a quantitative exposure assessment for the oxons would not be necessary and no additional fate data for these compounds would be needed. If toxicity of the oxons is shown to be important, then fate studies would be necessary to quantify potential oxon formation. If these new fate studies show that the oxons are formed in amounts that are too low to affect risk conclusions, then no further refinement would be necessary and additional fate and transport studies on the oxons would not be required. In all cases, if sufficient data are not available, risk assessments will be based on conservative assumptions.

Toxicity Data Justifications

In the absence of data, risk assessment will assume that the oxon degradates are of toxicological concern. It is anticipated that in future risk assessment, quantification of risk specific to the oxons will be implemented using either available toxicity data or established default assumptions. For example, the OP Cumulative Assessment assumed that the toxicity of oxons to mammals could be up to 100 times greater than that of the parent, and for frogs and aquatic invertebrates, the available data suggest that the ratio of the toxicity of the oxon relative to that of the parent may be more than for mammals. The Division will develop a set of standard default assumptions at a later date.