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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: March 16, 2011

SUBJECT: **Cryolite.** Human Health Assessment Scoping Document in Support of Registration Review.

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Executive Summary

The Health Effects Division (HED) Cryolite Registration Review Team has evaluated the most recent human health assessments and database for the insecticide cryolite to determine the scope of work necessary to support the established tolerances and existing registrations. The risk assessment used to support the 1996 Reregistration Eligibility Decision (RED) and a recent

aggregate assessment for fluoride were the primary sources for this evaluation. The Agency published a Reregistration Eligibility Decision (RED) in August 1996.

Cryolite is a naturally occurring mineral of sodium aluminum fluoride; products included in this registration review case include both natural and synthetic sources. Cryolite is an insecticide registered for use in agricultural settings to various fruits and vegetables, as well as some uses on ornamental plants. No new uses are pending at this time. There is not likely to be a residential exposure based on the registered use pattern, but there is a potential for occupational exposure. Cryolite degrades to fluoride in the environment so all food tolerances are expressed in terms of fluoride, and there could be exposure to fluoride in drinking water as a result of cryolite applications.

Sufficient data are available to assess the toxicity of cryolite and fluoride, with the exception of an immunotoxicity study and a subchronic inhalation toxicity study. The 1996 RED evaluated data on both cryolite and fluoride because cryolite's toxicity is attributed to its dissociation into fluoride ions. Data evaluated included guideline toxicity studies with cryolite, carcinogenicity studies with fluoride, and assessments by several government agencies on fluoride in drinking water. There is not likely to be significant dermal absorption from cryolite due to its ionic nature.

Fluoride is considered to have a U-shaped dose-response curve for oral health. In some areas of the country fluoride is added to the drinking water to prevent dental caries, but exposure to fluoride at higher levels can cause pitting of the teeth. Severe dental fluorosis, including enamel pitting and other effects, is the effect of concern from dietary exposure. The Office of Water has recently completed a benchmark dose analysis in order to select a point of departure based on severe dental fluorosis from exposure to fluoride. The reference dose for fluoride is 0.08 mg/kg bw/day, and is based on an epidemiological study of fluoride exposure and dental health.

Sufficient residue data are available for dietary risk assessment and tolerance assessment. In the most recent existing risk assessment for cryolite no dermal or inhalation endpoints of toxicological concern were identified; therefore, a quantitative risk assessment for occupational exposures was not completed. In the future, should applicable toxicity endpoints be defined, quantitative occupational risk assessments would need to be developed to assess applicable worker activities.

No new exposure data are required to assess occupational exposure. The existing registrants for cryolite are members of the Agricultural Reentry Task Force (ARTF) and the Agricultural Handlers Exposure Task Force (AHETF) so data from these efforts, coupled with the existing data already used by the Agency, may be used for any future quantitative assessment of occupational risks.

OPP has recently completed an aggregate risk assessment for exposure to fluoride, including the following sources of fluoride: dietary exposure from the pesticides cryolite and sulfuryl fluoride; water exposure from naturally occurring sources of fluoride in the environment as well as the intentional addition of fluoride to drinking water sources to prevent dental caries; incidental

ingestion of fluoride while brushing teeth; and soil ingestion by children. Exposures for some sub-populations exceeded the level of concern based on an endpoint of severe dental fluorosis. The Agency is currently seeking comment on this risk assessment (EPA Docket No. EPA-HQ-OPP-2005-0174). These comments, as well as any proposed risk mitigation, will be incorporated into a new risk assessment to support the registration review of cryolite.

Introduction

Cryolite [sodium aluminofluoride or sodium aluminum fluoride or sodium hexafluoroaluminate] is an insecticide used to control a variety of pests including various weevils, leaf rollers, various moth and worm species, and grape skeletonizers. Cryolite can be used on a wide array of agricultural crops including grapes (wine, table, raisin), cole crops, citrus, berries, tomatoes, cucumber, lettuce, and many types of ornamentals. Formulations include dusts, wettable powders, water dispersible granules, and baits/solids. Some formulations can contain as much as 96 percent active ingredient by weight. A recent evaluation of cryolite use indicates almost 2 million pounds per year are applied on about 300,000 acres, most of which are on grapes (92% of total pounds applied and 96% of treated acres) (Prieto, 2010). Use in California accounts for the vast majority of cryolite use (97%). In agriculture, groundboom, airblast, and aerial applications are typical but applications as a pure dust can also occur which may dictate other specialized forms of equipment being used. Applications to ornamentals may also be made using handheld equipment such as low and high pressure handgun sprayers and backpack sprayers. There are no cryolite containing products that appear to be marketed for sale to homeowners nor are there products which appear to be labeled for use by professionals in the residential marketplace (i.e., outdoors or indoors). Maximum application rates for most agricultural crops are in the 5 to 16 pounds product per acre range while some uses, especially on ornamentals can be higher (i.e., up to 30 lb/A using a 96% formulation).

Natural cryolite is a white, black, purple, or violet crystalline solid with a melting point of 1009 C; synthetic cryolite is a white crystalline solid with a melting point ranging from 960-1027C. Cryolite is only slightly soluble in water (<200 ppm at 25C) and is insoluble in alcohol. Cryolite decomposes in alkali.

Tolerances are established in 40 CFR §180.145(a)(2) for various fruits and vegetables for residues of fluoride as a result of cryolite application. HED recommended modifications to the tolerance levels in the RED and subsequent memoranda (Soderberg, 2001), but they have not been published as of January 20, 2011.

In 2006 the National Research Council (NRC) of the National Academies of Sciences (NAS) released a report on the toxicity of fluoride (*Fluoride in Drinking Water: A Scientific Review of EPA's Standards*) that recommends regulating fluoride based on severe dental fluorosis rather than crippling skeletal fluorosis, which was the endpoint used in prior cryolite dietary assessments. It should also be noted that there are oral health benefits associated with fluoride exposure at lower levels. The National Academies of Sciences Institute of Medicine has established an adequate intake level of 0.05 mg/kg/day (IOM, 1997). At beneficial levels,

fluoride reduces the incidence of dental caries by inhibiting the demineralization of enamel associated with the activity of cariogenic bacteria and by promoting rebuilding of demineralized enamel. The Office of Water conducted a benchmark dose analysis of an existing epidemiological study and selected a point of departure of 0.08 mg/kg/day on the basis of severe dental fluorosis. Further discussion of the endpoint may be found in the hazard section of this document.

The HED Registration Review Team has reviewed the most recent risk assessments and data received since the RED to determine if additional studies and/or risk assessments are needed to support the registration review of cryolite. In addition, the Office of Pesticide Programs has recently prepared a human health risk assessment for fluoride, which considers all sources of fluoride, including the pesticides sulfuryl fluoride and cryolite. Finally, the Team has conducted a screening-level literature search for any information that would aid in assessing human health risks to cryolite.

Hazard Identification/Toxicology

The 1996 RED evaluated data on both cryolite and fluoride because cryolite toxicity is attributed to its dissociation into fluoride ions. Data evaluated included guideline toxicity studies with cryolite, National Toxicology Program (NTP) carcinogenicity studies with fluoride, and assessments by several government agencies on fluoride in drinking water. In addition, HED has considered the 2006 National Academy of Sciences report described in the introduction of this document and the recent aggregate assessment prepared for sulfuryl fluoride.

Toxicity studies with cryolite evaluated for the previous RED include subchronic feeding studies in rats and dogs, a chronic feeding study in dogs, developmental toxicity studies in rats and mice, a range-finding developmental toxicity in rabbits, a 2-generation reproduction toxicity study in rats, and mutagenicity studies. Also evaluated were NTP carcinogenicity studies with sodium fluoride in rats and mice.

A dermal toxicity study is not available for cryolite but was not required in the 1996 RED because the charged nature of parent cryolite and degradate (fluoride ions) make extensive dermal absorption unlikely. A metabolism study with cryolite was not available but was not required because it is known that cryolite dissociates into fluoride. An immunotoxicity study and a subchronic inhalation toxicity study are now required for cryolite.

Dental lesions in rats and mice cryolite toxicity studies were due to enamel fluorosis and included effects such as attrition, deformity, mottling, and degeneration. Similar lesions were also noted in the rat and mice NTP studies with sodium fluoride. Fluoride can also accumulate in bone, and increased bone density in rats after treatment with cryolite was also noted.

Other toxicity from cryolite included hematological changes in dogs, rats, and rabbits. Cryolite treatment caused gastric erosions, ulcerations, and other stomach lesions in rats, mice, and rabbits due to irritation.

Mutagenicity studies with cryolite were negative. In the NTP rat study with sodium fluoride, osteosarcoma occurred in one mid-dose male and 3 high-dose males. No treatment related tumors were found in the NTP mouse study with sodium fluoride. The cancer classification was "not classifiable as to human carcinogenicity". This classification was supported by the National Research Council's review (i.e., the National Academy of Sciences Subcommittee of Health Effects of Ingested Fluoride Report) who concluded that "... the available laboratory data are insufficient to demonstrate a carcinogenic effect of fluoride in animals." and that "... the weight of evidence from more than 50 epidemiological studies does not support the hypothesis of an association between fluoride exposure and increased cancer risk in humans."

There was no increased fetal sensitivity noted in 3 developmental studies. No developmental toxicity occurred in the rat developmental toxicity study. Bent ribs and limb bones were found in the mouse developmental study at a maternally lethal dose. No developmental toxicity was noted in a rangefinding developmental toxicity study in rabbits at a maternally lethal dose.

There was qualitative sensitivity in the 2-generation reproductive toxicity study for cryolite with toxicity in pups (decreased body weight, pale kidneys/livers, and enlarged hearts) more severe than toxicity in adults (dental lesions). However, there was no quantitative sensitivity since toxicity in adults occurred at lower doses than in pups.

Acute and subchronic neurotoxicity studies are not available for cryolite. However, neurotoxicity was not observed in the available cryolite studies. Furthermore, since the residue of concern for cryolite is the fluoride ion, for which the most sensitive endpoint has been determined to be severe dental fluorosis based on extensive review of available data, more sensitive neurotoxic effects are not expected. Therefore, neurotoxicity studies are not required for cryolite.

The recent aggregate risk assessment for fluoride included a lengthy analysis for potential sensitivity of children to fluoride, and concluded:

> "Given the relative completeness of the fluoride toxicology database, the use of a children-specific endpoint that is the most sensitive effect and well-documented outcome in the literature, the data indicating that there is a U-shaped dose-response curve for oral health, and our understanding of the potential exposures to fluoride, the OPP is reducing the FQPA Safety Factor for fluoride to 1X."

Since the toxicity of cryolite results from release of fluoride ions, these conclusions also apply to cryolite.

HED has recently completed an aggregate risk assessment for all sources of fluoride (Doherty, 1/7/11); this assessment considered only oral exposure since dermal hazard is expected to be minimal. A benchmark dose analysis was conducted by the Office of Water, who selected a reference dose (RfD) of 0.08 mg/kg/day, based on an endpoint of severe dental enamel fluorosis. An epidemiological study of fluoride exposure and dental health was used as the basis for the

RfD (Dean, 1942). This RfD is protective of all populations.

Conclusions. The toxicity database for cryolite is considered complete with the exception of the immunotoxicity and subchronic inhalation toxicity studies. The FQPA safety factor is reduced to 1X for the reasons noted above. Once the requested studies are received endpoint selection for cryolite should be revisited.

Dietary Exposure

Tolerances are established for residues of cryolite 40 CFR 180.145 for various fruit and vegetable commodities. The residue of concern for dietary risk assessment and the tolerance expression for cryolite is fluoride. Although uses of cryolite are registered for a few crops with animal feed commodities, the Agency had previously determined that there is no reasonable expectation of finite residues in livestock; therefore, livestock commodity tolerances are not needed.

Crop field trials requested in the RED have been received and reviewed. No additional residue chemistry data are required to support the existing uses of cryolite. Modifications to the tolerance values listed in 180.145 are needed as described in the Tolerance section below.

HED has recently completed a dietary exposure assessment for all sources of fluoride in food and drinking water, including the pesticides cryolite and sulfuryl fluoride (Doherty, 1/7/11). Monitoring data were used to account for residues of fluoride as a result of cryolite application; residues in grapes and raisins were higher than other crops, which is consistent with BEAD's usage assessment. High quality monitoring data were also used to assess exposure to fluoride in drinking water, including intentional addition of fluoride to prevent dental caries as well as naturally-occurring sources of fluoride.

Conclusion. No additional residue data are needed to support the registration review of cryolite. Since fluoride is the only residue of concern from cryolite applications, HED will determine if a revised assessment is needed once all of the comments have been received on the aforementioned aggregate assessment.

Residential Exposure

Cryolite containing products are not marketed for sale to homeowners nor do the products appear to be intended for use by professionals in a residential setting. As such, risks from residential exposures have not been considered in previous assessments nor would they be considered at this time. However, it should be noted that there are ongoing activities related to refining the methods used to complete residential exposure assessments (e.g., updates to *SOPs for Residential Exposure Assessment* and issues related to chemical trespass such as spray drift). In the future, possible cryolite exposures would be considered based on any applicable changes in the standard methods used to evaluate residential exposures.

Conclusion. No residential data gaps were identified during the *Registration Review* scoping process for cryolite, as these types of exposures are not anticipated.

Aggregate Risk Assessment

An aggregate risk assessment was recently completed for fluoride (Doherty, 1/7/11), which considered the following exposures:

- food exposure from use of cryolite as a pesticide;
- food exposure from use of sulfuryl fluoride as a pesticide;
- naturally-occurring sources of fluoride in drinking water;
- intentional addition of fluoride to drinking water to prevent dental caries;
- incidental ingestion of toothpaste while brushing teeth;
- background levels of fluoride in food and beverages; and
- incidental ingestion of soil and outdoor dust.

The most recent aggregate assessment did identify some sub-populations whose exposure exceeded the Agency's level of concern for fluoride, particularly children living in areas with high levels of naturally-occurring sources of fluoride in their drinking water. EPA is seeking public comment on this risk assessment and opportunities for mitigation and refining of the assessment (EPA Docket No. EPA-HQ-OPP-2005-0174). These comments, as well as future refinements to the aggregate assessment, will be incorporated in any future risk assessments prepared to support the registration review of cryolite.

The upcoming policy revisions in the SOPs for residential exposure assessment and other related policies may also require revisions to the residential assessment, in which case a new aggregate assessment may be required.

Cumulative Risk Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to cryolite and any other substances. As described in the aggregate section above, fluoride is a degradate of cryolite, and has been previously assessed. For the purposes of this registration review assessment of data needs EPA has not assumed that cryolite has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Occupational Exposure

Due to the manner in which cryolite is used, occupational exposures would be anticipated for those involved in the application process (e.g., applying by ground sprayer) and for those who are working in fields which have been previously treated with cryolite (e.g., harvesting). Assessments evaluate the potential risks for these types of activities if an appropriate toxicological endpoint is associated with a chemical. However, in the most recent existing risk assessment for cryolite no dermal or inhalation toxicological endpoints were identified; therefore, a quantitative occupational risk assessment for occupational exposures was not completed. Toxicity via the dermal route is not expected due to the ionic nature of cryolite, but a subchronic inhalation toxicity study is outstanding. If an applicable endpoint is identified in this study then a quantitative risk assessment for occupational exposures will be conducted.

Conclusion. No occupational data gaps were identified during the Registration Review scoping process for cryolite because the registrants are members of the ARTF and AHETF[1], which would address future data requirements. Additional scenarios may be needed to address changes in other risk assessment policies and methodologies related to spray drift, worker protection and volatilization of pesticides that may necessitate the need for additional data. An occupational risk assessment may be needed if applicable endpoints are identified in the outstanding inhalation toxicity study.

Public Health and Pesticide Epidemiology Data

The Agency conducted an analysis of incidents related to cryolite use since 2002 (Recore, 11/30/10). There are no cryolite cases reported in the main or aggregate Incident Data System (IDS) databases; therefore, there does not appear to be a concern at this time that would warrant further investigation. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.

Tolerance Assessment and International Harmonization

A summary of the existing tolerances may be found in Table 2 in the appendix. No maximum residue limits (MRLs) have been established by Codex or Canada (M. Negussie, 11/15/10, personal communication) for residues of cryolite or fluoride. Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

After reviewing data submitted in response to the RED, HED recommended several changes to the residue definition and residue values. Should the aggregate risk issues described above be resolved, HED recommends that the residue definition be modified in accordance with the guidance issued in 2009 (S. Knizner, 5/27/09). Since the residue of concern from both sulfuryl fluoride and cryolite applications is fluoride, the risk assessment teams for both chemicals will work together to develop an appropriate tolerance definition. Modifications to the recommendations on the tolerance levels recommended in the RED may be required.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.epa.gov/compliance/resources/policies/ej/exec_order_12898.pdf. The Office of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S. (including different ages, regions, and ethnicities), and people who may be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

Human Studies

This risk assessment does not rely on any data from studies in which human subjects were intentionally exposed to a pesticide or other chemical.

Endocrine Disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Cryolite is not among the group of 58 pesticide active ingredients on the initial list to be

screened under the EDSP. Under FFDCA sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

Data Requirements

No occupational/residential or dietary exposure data are needed at this time. The following toxicity studies are required:

- 870.3465 Subchronic Inhalation Toxicity Study
- 870.7800 Immunotoxicity Study

The rationales for requiring these studies are attached to this document.

References

Author	DP Barcode/ Record No.	Date	Title
M. Doherty	385539	1/7/11	Sulfuryl Fluoride -Revised Human Health Risk Assessment for Fluoride to Incorporate New Hazard and Exposure Information
S. Recore	383619	11/30/10	Cryolite: Review of Human Incidents
R. Prieto	NA	11/10/10	BEAD Chemical Profile for Registration Review: Cryolite (075101)
D. Soderberg	279011	12/18/01	Cryolite (List A). Summary of Issues on Tolerance Reassessment
S. Knizner	NA	5/27/09	Interim Guidance on Tolerance Expressions
IOM	NA	1997	Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Institute of Medicine. Washington, DC: National Academy Press.
L. Rossi	EPA-738-R-96-016	August, 1996	Reregistration Eligibility Document: Cryolite
T. Myers	Acc. # 011895	2/14/96	The HED Chapter of the Reregistration Eligibility Decision Document (RED) for Cryolite (Case No. 0087; Chemical No. 075101)
H.T. Dean	NA	1942	*The Investigation of Physiological effects by the Epidemiology Method. In: Fluoride and Dental Health.* Washington, DC: American Association for the Advancement of Science. No. 19. pp 23-31.

Attachments

Chemical Identity

Table 1. Chemical Identity	
Common Name	Cryolite
Other Names	Aluminum sodium fluoride; Sodium hexafluoroaluminate; Aluminate(3-), hexafluoro-, trisodium, (OC-6-11)-; trisodium hexafluoroaluminate(3−)
PC Code	075101
CAS registry number	15096-52-3; 13775-53-6 [1]
Case No.	0087
Chemical Structure	Na_3AlF_6 

[1] The first CAS number is for the mineral cryolite; the second number refers to the inorganic compound aluminum sodium fluoride (synthetic cryolite).

Table 2. Summary of US Tolerances [1]		
Commodity	**Current Tolerance, ppm**	**Reassessed Tolerance[2], ppm**
Tolerances listed under 180.145 (a)(1)		
Apricot	7	10
Berries	None	0.5
Blackberry	7	Revoke – new berry crop group
Blueberry	7	Revoke – new berry crop group
Boysenberry	7	Revoke – new berry crop group
Broccoli	7	7
Brussels sprouts	7	7
Cabbage	7	45
Cauliflower	7	7
Collards	7	35
Cranberry	7	2
Cucumber	7	4
Dewberry	7	Revoke
Eggplant	7	30
Fruit, citrus	7	95
Grape	7	7
Grape, raisin	None	30
Kale	7	35
Kohlrabi	7	7
Lettuce, head	7	180

Lettuce, leaf	7	40
Loganberry	7	Revoke – new berry crop group
Melon	7	7
Mint, hay	None	35
Nectarine	7	10
Peach	7	10
Pepper	7	7
Plum, prune, fresh	7	2
Plum, prune, dried	None	7
Pumpkin	7	7
Raspberry	7	Revoke – new berry crop group
Squash, summer	7	7
Squash, winter	7	7
Strawberry	7	7
Tomato	7	30
Tomato, paste	None	45
Watermelon	None	7
Youngberry	7	Revoke – new berry crop group
Tolerances listed under 180.145 (a)(2)		
Potato	2	2
Potato, processed potato waste	22	22
Tolerances listed under 180.145 (c)		
Kiwifruit	15	8

[1] No maximum residue limits have been established by Codex and Canada for residues of fluoride. Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[2] Tolerance reassessment recommendations from D. Soderberg memo of 12/18/01, barcode D279011.

Rationale for Requiring a Subchronic Inhalation Toxicity Study

Guideline Number: 870.3465 **Study Title: Subchronic Inhalation Toxicity Study**
Rationale for Requiring the Data
This data requirement is conditionally required under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). This study is required for cryolite because workers can potentially be exposed to cryolite via the inhalation route of exposure. Cryolite is in toxicity category IV for inhalation exposure and showed little potential for irritant action in other acute studies: cryolite was in toxicity category III for eye irritation and toxicity category IV for dermal irritation. However, there are concerns for portal of entry effects by the inhalation route because cryolite caused gastric erosions and ulcerations in a subchronic feeding study in rats.
Practical Utility of the Data
How will the data be used? This study can be used to select endpoints and doses for use in exposure assessment for workers by the inhalation route of exposure. **How could the data impact the Agency's future decision-making?** This study will be used in a worker occupational exposure assessment. An inhalation exposure assessment was not conducted in the previous risk assessment. The risk assessment will need to be revised after an inhalation exposure assessment is completed.

Rationale for Requiring an Immunotoxicity Study

Guideline Number: 870.7800 **Study Title: Immunotoxicity**
Rationale for Requiring the Data
This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies assessing functional immunotoxic endpoints are helpful in fully characterizing a pesticide's potential immunotoxicity. These data will be used in combination with data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies to characterize potential immunotoxic effects.
Practical Utility of the Data
How will the data be used? These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have these data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

[1] United Phosphorus Inc. is not a member of AHETF so data compensation could apply if these data were used to evaluate their product.