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PROBLEM FORMULATION DOCUMENT

ALLYL ISOTHIOCYANATE

November 16, 2018

Introduction

The Department of Pesticide Regulation (DPR) has initiated a comprehensive risk and exposure assessment of the active ingredient allyl isothiocyanate (AITC). In addition to DPR's policy to conduct a risk assessment for any new active ingredient proposed to be used as a fumigant, DPR has concerns about acute and chronic exposures to this pesticide and has identified potential adverse health effects in studies sufficient to initiate the risk assessment process. The first step in this process is to develop a Problem Formulation Document that provides a scope for the risk assessment, potential exposure scenarios, and future mitigation activities that may be proposed. DPR expects the scope of the risk assessment for AITC to be typical for any pre-plant fumigant applied to agricultural fields.

Background

Risk assessment plays a critical role in DPR's evaluation of the potential human health hazards associated with pesticide exposure. The breadth and depth of the risk assessment depends on the data available and the level of concern DPR has for adverse effects of the pesticide. The toxicological effects are identified by a review of studies DPR requires from the registrants and peer-reviewed literature. The exposure assessment may be a simple assessment based on readily available data and conservative assumptions (screening-level assessment) resulting in point estimates for exposure assessment. If DPR believes a more refined assessment is necessary, then DPR may rely on data specific to the pesticide and the exposure scenario as well as complex models to generate a refined exposure assessment for each identified exposure scenario. To support DPR's decision-making, staff may assess potential dietary (food and drinking water), workplace, residence, and ambient air exposures.

DPR initiates a Problem Formulation/Scoping phase prior to drafting a risk assessment. During this phase, risk assessors and risk managers within DPR meet and discuss the scope of the risk assessment for a specific pesticide. Information and data relevant to the pesticide is reviewed and evaluated to determine the scope of the risk assessment. The information and data that may be evaluated during the process include: toxicology, pesticide use reports, pesticide sales, illness reports, monitoring data, primary uses of the pesticide, exposure scenarios identified on the labels, potential exposure pathways, available adverse effects reports, relevant United States

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Environmental Protection Agency (U.S. EPA) risk assessments, important sources of uncertainty and variability in the data, and potential mitigation options.

The internal problem formulation/scoping discussions resulted in this Problem Formulation Document and a diagram of exposure pathways (Figure 1) for AITC. This document will be presented to the Pesticide Registration and Evaluation Committee (PREC) for the committee's comments, as well as posted on DPR's website for public comment. The public comment period is 60 days after posting the documents. All written comments submitted to DPR will be considered in the preparation of the Risk Characterization Document (RCD).

1. Reasons for entering the risk assessment process

It is DPR's practice to conduct a risk assessment on new fumigant active ingredients. In addition, DPR has concerns about the potentially adverse health effects of AITC identified in animal studies. These concerns include:

- reproductive effects
- genotoxicity, and
- oncogenicity

2. Adverse effects and illness reports

- a. As required by Food and Agricultural Code section 12825.5, registrants of AITC products notify DPR of adverse effects. California has not registered any AITC products. The United States Environmental Protection Agency (U.S. EPA) has registered at least one product containing AITC. DPR staff reviewed the potential adverse effects submitted from 2005 – 2017. There were no adverse effects reported during this period.
- b. DPR staff reviewed the Pesticide Illness Surveillance Program (PISP) database for AITC. There were no reports of illness linked to this active ingredient in the database.

3. Potential toxicological effects

The effects observed after oral or inhalation exposure of laboratory animals to AITC included, but were not limited to, the following:

- a. Local effects at the nasal mucosa – metaplasia, and ulceration of nasal epithelium in rats
- b. Neurotoxicity – decreased motor activity and atrophy of olfactory bulb in the brain in rats

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- c. Genotoxicity – in genotoxicity testing studies, AITC was positive for causing gene mutation, chromosomal damage, and tumorigenicity in vitro in mammalian cells.
- d. Oncogenicity – urinary bladder tumors in rats
- e. Reproductive toxicity – cataracts and retinal dysplasia in offspring of treated rats and decreased neonatal survival.
- f. The Toxicity ForeCaster (ToxCast™) and Tox21 high-throughput screening assays (HTS) were examined for indications of pathway disruptions that could lead to toxic effects. AITC was active in assays for molecular targets, such as the nuclear receptors PPAR α , and RXRB, which is involved in cellular metabolism.

4. Primary uses in California

Products containing AITC are not currently registered for use in California. Therefore, no pesticide use reports exist for AITC. The scope of this problem formulation document and the expected Risk Characterization Document will be the use of synthetic AITC as a soil fumigant. Synthetic or natural oils of mustard will not be included in the scope of the risk assessment.

5. Exposure scenarios to be considered in the exposure assessment

DPR expects AITC products to be used to fumigate soils prior to planting a crop. Staff will develop exposure scenarios common to other pre-plant soil fumigants used in California. These scenarios will include AITC handlers, re-entry workers, and residents/bystanders.

6. Potential exposure pathways diagram (conceptual model)

Figure 1 shows a diagram of potential exposure pathways (i.e., conceptual model) of human exposure to AITC containing products. Based on its expected fumigant uses, routes of exposure will be primarily inhalation and dermal. Near field computer models and/or monitoring data will be used for characterizing the amount of pesticides released into the exposure media (e.g., air) and eventually received by the receptor of interest (e.g., pesticide handlers, re-entry workers, occupational bystanders and residential bystanders including children). As AITC exposure data is not available, exposures of pesticide handlers and re-entry workers will be assessed using surrogate exposure data for other fumigants. Occupational and residential bystander exposures will be assessed using computer models such as American Meteorological Society/Environmental Protection Agency Regulatory Model (AERMOD).

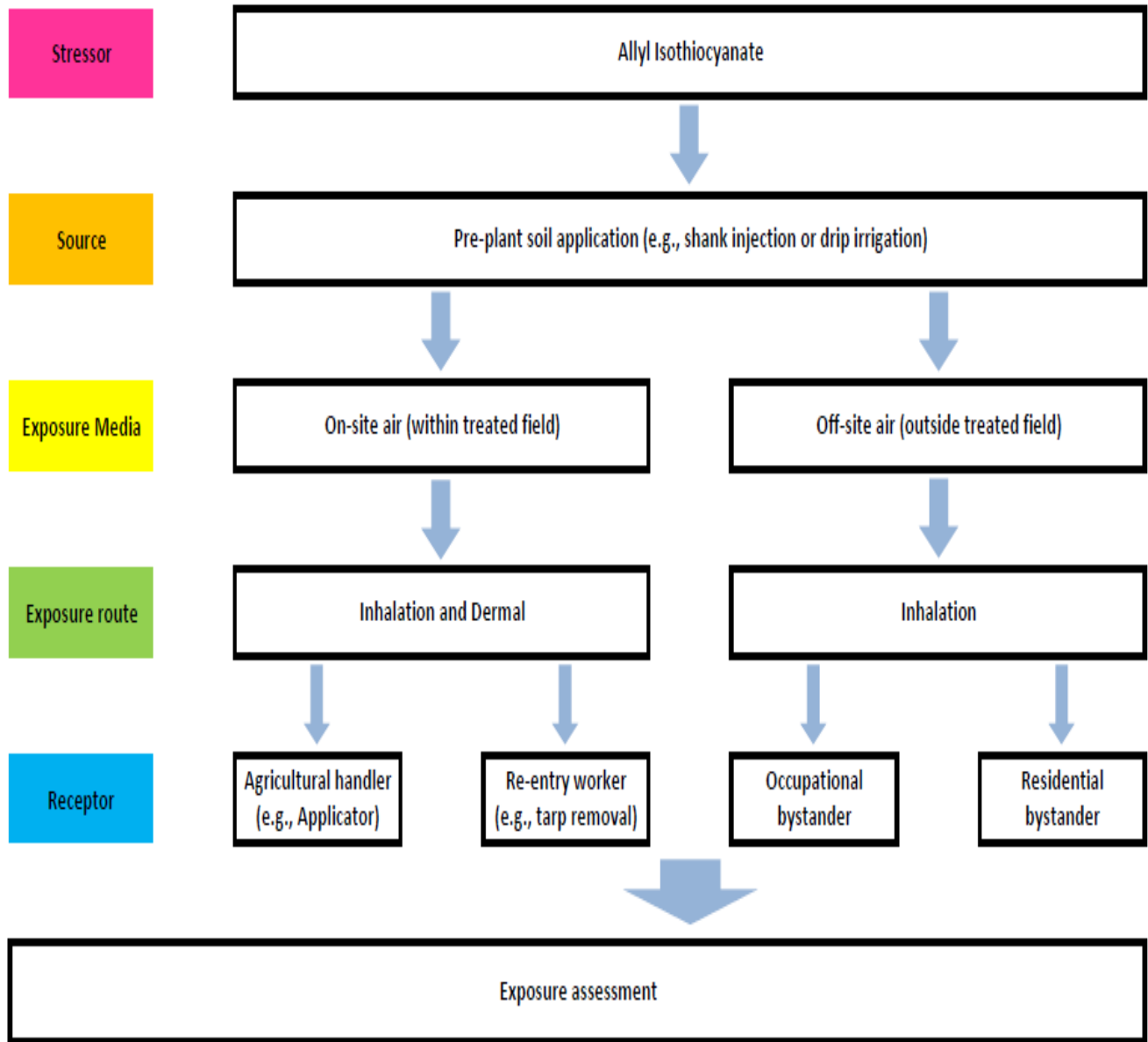


Figure 1. Potential exposure pathways of AITC containing products in humans.

7. Potential mitigation measures to be considered for evaluation in the risk assessment

The risk assessment will consider the ability of reduced application rates, reduced number of applications, buffer zones, and personal protective equipment to mitigate risks identified in the RCD.

8. Data gaps

No data gaps have been identified in the toxicologic database for AITC at this time. This problem formulation considered all pertinent data for establishing relevant sources, media, and routes of human exposure to a pre-plant soil fumigant (i.e., exposure scenarios). The existing data are sufficient for identifying important exposure scenarios presented in Figure 1 (i.e., no data gap). However, additional data may be needed to conduct in-depth or refined analysis of the aforementioned exposure scenarios.

9. Analysis plan

For the Toxicology Profile and Hazard Identification, DPR's Human Health Assessment Branch (HHA) plans to identify the main toxicological effects and the points of departure (PoD) according to the relevant route of exposure from the following sources:

- Toxicological studies submitted to DPR by the registrant or published in the literature;
- Existing human health risk assessments by other regulatory agencies including U.S. EPA, EU, Australia and Canada.

For risk characterization, HHA will use the relevant PoDs and measured or estimated exposures to estimate non-cancer Margins of Exposure (MOEs) and/or cancer risk. These risk estimates will be compared to selected target MOEs.

HHA will inform the risk manager of the confidence it has in the risk estimates by discussing overall uncertainty and variability in the risk assessment.

Following review by the Office of Environmental Health Hazard Assessment (OEHHA), U.S. EPA, registrants and other interested parties, DPR will respond to reviewers and generate a finalized risk assessment document.

10. Timeline for completion of the Risk Characterization Document

The Human Health Assessment Branch plans to complete the draft RCD by January 2020.

11. References:

U.S. EPA 2012. Standard Operating Procedures for Residential Pesticide Exposure Assessment (Revised October 2012). In *Residential SOPs*, pp. 582.

U.S. EPA 2013. Office of Pesticide Programs, Part 158 Toxicology Data Requirements: Guidance for Neurotoxicity Battery, Subchronic Inhalation, Subchronic Dermal and Immunotoxicity Studies. May 1, 2013.

12. Comments

This Document will be posted on DPR's website as a draft on our Risk Characterization Document page (https://www.cdpr.ca.gov/docs/whs/active_ingredient/aitc.htm) for public viewing after being presented to the Pesticide Registration Evaluation Committee. The comment period is open for 60 days. After the comment period, the Problem Formulation Document will be posted as a final document. Please send written comments to:

Risk Assessment – Allyl Isothiocyanate
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Comments will be reviewed and where appropriate, technical suggestions will be incorporated into the text of the draft RCD.