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SUBJECT: Charge Questions relating to DPR's Draft Risk Characterization Document for Allyl Isothiocyanate (July 2020)

On July 31, 2020, the Department of Pesticide Regulation (DPR) sent the draft Risk Characterization Document (RCD) for Allyl Isothiocyanate (AITC) to the Health Effects Division of the Office of Pesticide Programs at the U.S. Environmental Protection Agency for review. The RCD focuses on the potential toxicity of AITC by the inhalation route to align with its proposed use as a chemical fumigant in California. Risks from non-oncogenic effects were estimated in terms of margins of exposure (MOEs) to workers, occupational bystanders, and residential bystanders. Because AITC is not yet registered, two novel exposure assessment approaches were applied, one involving surrogate data to estimate worker exposure and the other using an air dispersion model to estimate bystander exposures.

This memorandum provides charge questions to the reviewers pertaining to decision points in the assessment that we consider to be the most consequential in terms of the ultimate risk estimates. Reviewers are requested to determine whether the scientific work product is based upon sound scientific knowledge, methods, and practices. Comments on areas outside the charge questions are also welcome.

Toxicity

All critical points of departure (PODs) for this risk assessment were established from inhalation studies in rats. However, the AITC inhalation toxicity database was limited, consisting of only three inhalation studies in rats (two acute and one subchronic). In addition, no human inhalation studies for derivation of the PODs were identified by systematic review and no inhalation studies were available to determine toxicokinetics, reproductive or developmental toxicity, chronic toxicity or oncogenicity. A number of oral toxicity studies in laboratory animals were available and were used to inform AITC's toxicokinetics, oncogenicity, and developmental toxicity.

Hazard Identification

1. **Acute POD: A default 10x LOEL-to-NOEL extrapolation factor was used to establish the critical acute POD of 2.5 ppm**

The critical study was a whole body inhalation toxicity study in rats exposed for 4 hours to vaporized AITC. This study did not inculde a no observed effect level (NOEL). The effects at the lowest tested dose (LOEL of 25 ppm) included decreased rearing counts and decreased motor activity. A benchmark dose (BMD) modeling approach was not used to establish the acute POD for AITC because the high variability in the data for the critical endpoints was not conducive to such modeling. Instead, a default dose extrapolation factor of 10 was used to establish the critical POD.

2. **The critical chronic inhalation POD was estimated from the subchronic critical POD by applying a default duration extrapolation factor of 10. This was necessitated by the lack of chronic inhalation studies.**

The critical chronic inhalation POD of 0.5 ppm was derived from the subchronic critical POD of 5 ppm. The latter was established from a 13-week inhalation toxicity study in rats. The effects at the LOEL of 10 ppm resulted from both portal of entry (metaplasia of the respiratory epithelium, degeneration of the olfactory epithelium) and systemic (decreased motor activity) delivery to the target sites. When a 13-week subchronic study is used for duration extrapolation, a factor of 3 may be considered because the study covers substantial portion (about 13%) of the 2-year rat lifetime. However, we applied the full default value due to the limited inhalation database.

3. **PODs from oral studies were not used to establish critical PODs**

Effects seen in oral studies of short-term, subchronic, and chronic durations in laboratory animals included hyperplasia of the stomach and urinary bladder epithelium, and cataracts in rats. These effects were not observed in the acute and subchronic inhalation studies in rats. Therefore, oral PODs were not used to establish critical inhalation PODs due to concerns about route specificity of observed effects.

However, when we converted the oral PODs to inhalation PODs using duration adjusted default rat breathing rates, we determined that the equivalent external air concentrations derived from the oral studies showed effects at concentrations similar to those in the inhalation studies. For example, the subchronic oral NOEL of 6.6 mg/kg/day for urinary bladder hyperplasia in rats established in a 13-week drinking water study produced an equivalent external air concentration of 9.5 ppm. This value was similar to the estimated critical subchronic inhalation POD of 5 ppm in rats for motor activity decrements. The same route extrapolation was performed on the chronic

oral POD of 0.6 mg/kg/day for urinary bladder hyperplasia in rats exposed for 2 years by drinking water. The resultant chronic equivalent external air concentration of 0.9 ppm was similar to the estimated critical chronic inhalation POD of 0.5 ppm for motor activity decrements. Because urinary bladder hyperplasia was the most sensitive systemic endpoint in the oral studies, this analysis showed that the critical inhalation PODs would be protective of any systemic toxicity induced by AITC.

4. **This RCD did not include a cancer risk estimate for AITC**

Chronic inhalation studies were not available to indicate if AITC has the potential to cause tumors by the inhalation route. However, orally administered AITC appeared to increase the incidence of three types of tumors in rats: undifferentiated leukemia, fibrosarcoma, and urinary papilloma.

Undifferentiated leukemia: This tumor was observed in one oral oncogenicity bioassay. However, there was compelling evidence that the observations were artifacts of the study design and the selected rat stain (F344/N) rather than AITC treatment.

Fibrosarcomas: This tumor was observed in a two year oral gavage study using rats. A role for AITC in fibrosarcoma induction was considered plausible. However, cancer potency analysis was precluded by the fact that the apparent effect occurred only at the high dose.

Urinary bladder tumors: This tumor was observed in two oral oncogenicity bioassays in rats. However, AITC by the inhalation route did not induce urinary bladder hyperplasia after 13 weeks of exposure. This observation suggested that bladder effects were relevant to oral, but not inhalation exposures. Consequently, urinary bladder epithelial hyperplasia and bladder tumors induced by chronic oral exposure were unlikely to result from inhalation exposure. As a result, bladder tumor data were not used to calculate a cancer potency value.

Exposure Assessment

5. **Due to a lack of AITC exposure monitoring data, worker exposures to AITC were estimated using exposure monitoring data from 1,3-dichloropropene (1,3-D) and chloropicrin.**

As described in the draft Exposure Assessment Document (EAD, Appendix 1 of the draft RCD), worker exposures to AITC were assessed for three application methods (shallow shank, deep shank, and drip). DPR used worker exposure monitoring data from chloropicrin to assess AITC worker exposures for all exposure scenarios except for loaders. For the loaders, 1,3-D data was used since no chloropicrin exposure monitoring data were available.

The chloropicrin or 1,3-D air concentrations measured at the worker breathing zone were corrected for recoveries and adjusted to the maximum AITC application rates for different application methods (shallow shank, deep shank, and drip).

Due to the lack of AITC data, the adjusted 1,3-D or chloropicrin air concentrations were used as a conservative measure to estimate worker exposures to AITC. The underlying assumptions and rationales are discussed in detail in the Exposure Appraisal section of the draft EAD (see Appendix 1 of the draft RCD).

6. **DPR estimated bystander exposures to AITC using an air dispersion model (AERMOD). Occupational bystander exposures were estimated at the field edge, and residential bystander exposures were estimated at 25 and 100 ft from the field edge.**

AERMOD employs hourly soil emission rates of a fumigant to estimate air concentrations at different distances from a treated field. DPR conducted AERMOD modeling for five different application and tarp methods, two of which used AITC-specific soil emission data. For the other three methods that lacked AITC specific data, 1,3-D and chloropicrin were used as surrogates. The complete review of 1,3-D and chloropicrin emission data is found starting on page 37 of the draft EAD (see Appendix 1 of the draft RCD). The rationale for selecting 1,3-D and chloropicrin data as a conservative measure when AITC data were not available is also discussed.

As AITC is not yet registered for use in California, DPR conducted AERMOD modeling in 5 regions where soil fumigants are currently applied (Central Valley, Central Coast, South Coast, Inland Empire and the Northern region), and used meteorological data from 6 weather stations (Merced, Kern, Santa Cruz, Ventura, Riverside, Siskiyou) within these five regions. Details on the modeling methodologies and the rationales of choosing these specific model input files are provided starting on page 65 of the draft EAD (see Appendix 1 of the draft RCD).

Risk Characterization

7. **Dosimetric adjustments of air concentrations to account for pharmacokinetic differences between laboratory animals and humans were used to calculate reference concentrations (RfCs) and risk targets (*i.e.*, target Margins of Exposure)**

The critical PODs from the selected animal studies were converted to human equivalent concentrations (HEC or POD_{HEC}) using dosimetric adjustment factors based on the US EPA reference concentration (RfC) methodologies.

Reference Concentrations: For RfCs calculated from HECs, the conventional interspecies uncertainty factor of 10 was reduced to 3 because the interspecies pharmacokinetic differences were considered resolved by the HEC conversion, regardless of whether the effects were portal of entry or systemic. The remaining default interspecies pharmacodynamic UF of 3x was retained because data relating to tissue level interactions were insufficient to quantitatively resolve potential animal-to-human differences. The full 10-fold intraspecies (UF_H) factor was also retained to reflect the range of sensitivity within the human population.

Target Margin of Exposure: The target MOE for AITC was equivalent to the UF_{TOTAL} of 30. This target MOE was considered adequate to protect human health for all potentially exposed populations (handlers, re-entry workers, occupational bystanders, and residential bystanders).

Worker and Bystander MOEs

8. **Risks to workers were estimated for acute (short term), subchronic (seasonal) and chronic (annual, lifetime) exposures.**

Under short-term, seasonal, and annual exposure conditions, worker MOEs for many scenarios were lower than the target of 30.

9. **Risk to occupational and residential bystanders, were estimated for acute exposures.**

Under short-term exposure conditions, all occupational and residential bystander MOEs were lower than the target of 30.

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