Pesticide Exposure and Risk Assessment Evaluation

Document Review

Department of Pesticide Regulation's Draft Risk Characterization and Exposure Assessment for Allyl Isothiocyanate

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Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
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PREFACE

Under the authority of California Food and Agricultural Code Section 11454.1, the Office of Environmental Health Hazard Assessment (OEHHA) conducts scientific peer review of human health risk assessments prepared by the Department of Pesticide Regulation (DPR). DPR reports the risk assessment in two documents:

- The Risk Characterization Document (RCD), which summarizes the toxicology database of the chemical; discusses hazard identification and dose-response analyses; assesses dietary exposure, when appropriate; and characterizes the risk associated with the various exposure scenarios (dietary, occupational, residential, and aggregate exposures).
- The Human Exposure Assessment Document (EAD), which describes non-dietary exposure scenarios and estimates exposure levels of on-site and off-site workers and residents.

This report is a review of both the draft RCD and draft EAD for the pesticide allyl isothiocyanate (AITC) provided by DPR (dated and received July 31, 2020). The draft EAD was included as Appendix 1 in the draft RCD.

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I. SUMMARY OF REVIEW AND MAJOR RECOMMENDATIONS

This report presents the review by the Office of Environmental Health Hazard Assessment (OEHHA) of the Department of Pesticide Regulation's (DPR) draft Risk Characterization Document (RCD) for allyl isothiocyanate (AITC), a pre-plant soil fumigant being evaluated for registration in California. The draft RCD characterized human health risks from AITC arising from its proposed use as a soil fumigant. Risks were assessed for acute, seasonal, and chronic exposures to on-site workers, and acute-only exposures to off-site workers and residential bystanders (child and adult).

Overall, we find the document to be well written. A thorough evaluation of available literature was provided, along with complete descriptions of the toxicological profile and exposure assessment. The rationale for evaluating only inhalation toxicity studies was provided, with comparisons to oral toxicity studies when appropriate; however, OEHHA recommends DPR further evaluate available non-inhalation data as significant data gaps exist for inhalation toxicity. We agree with DPR's choice of acute and chronic inhalation points of departure (PODs), but suggest the subchronic POD be re-evaluated to ensure the most health-protective value is chosen. After reviewing the available animal studies and genotoxicity evidence, OEHHA suggests that a cancer risk estimate should be developed for AITC. In light of data gaps for both route-specific toxicity and developmental neurotoxicity, OEHHA recommends increasing the uncertainty factor for intraspecies pharmacokinetics to 2, and adding an uncertainty factor of 3 to protect infants and children from pre- and post-natal effects following inhalation exposure to AITC. To protect on-site workers, OEHHA suggests the evaluation of potential dermal exposures to AITC in soil. To protect off-site workers and residential bystanders, OEHHA suggests estimating annual and lifetime exposures to AITC.

Our principal comments and major recommendations are summarized here in Section I. OEHHA's review focuses on those issues that are likely to impact the key findings and conclusions of the assessment. Detailed comments are provided in Section II. Responses to DPR's charge statements (descriptions of scientific assumptions, findings and conclusions to be addressed by peer reviewers) are provided in Section III, and minor comments are provided in Section IV.

A. Toxicity Evaluation

1. The draft RCD adequately described the oral toxicity database, and studies from the oral toxicity database were used to satisfy the data requirements for registration, yet only the limited inhalation toxicity database was considered

for establishing critical PODs. The reason cited was concerns about route specificity of observed effects.

OEHHA disagrees that there is sufficient evidence from the inhalation toxicity studies or from other metabolism and toxicokinetic studies to make the determination that effects observed in the oral studies would not occur by inhalation.

2. OEHHA agrees with the acute POD of 2.5 ppm based on decreased motor activity in rats following a single 4-hour nose-only exposure to AITC vapor (Herberth et al., 2017) at a lowest-observed-adverse-effect level (LOAEL) of 25 ppm, and the application of a 10-fold LOAEL-to-NOAEL (no-observed-adverse-effect level) extrapolation factor. This is the lowest acute POD from the database available.

3. The draft RCD selected a subchronic POD of 5 ppm based on neurotoxicity and histopathological changes in the olfactory epithelium from a subchronic inhalation study (Randazzo et al., 2017). It also pointed out that the lowest subchronic oral NOAEL of 6.6 mg/kg-day for bladder hyperplasia from Hasumura et al. (2011) is equivalent to an air concentration of 9.5 ppm which is higher than the determined POD. However, benchmark dose (BMD) modeling was not presented for the oral endpoint. OEHHA modeled the data with a benchmark response of 5% and derived BMDL's lower than the selected study NOAEL (see section II.A.1.c for detailed information). OEHHA recommends DPR re-evaluate the endpoints from the oral toxicity study using BMD, and choose the subchronic POD that is the most health protective, after taking into account route-specific issues (e.g., toxicokinetics).

4. OEHHA agrees with DPR's approach in deriving a chronic POD from a subchronic inhalation or oral POD by the application of a 10-fold study duration extrapolation factor.

5. The draft RCD did not include a cancer risk estimate for AITC. AITC induced treatment-related increases of undifferentiated leukemia and urinary bladder transitional-cell papilloma in male rats (NTP, 1982). OEHHA believes a quantitative assessment of cancer risk posed by AITC should be included.

B. **Risk Characterization**

1. OEHHA disagrees with the reduction of the intraspecies pharmacokinetic UF from a value of $\sqrt{10}$ to 1 for all effects, because the regional gas dose ratio (RGDR) approach does not consider the role of metabolism and excretion. Thus, OEHHA recommends that DPR retain the intraspecies pharmacokinetic

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uncertainty factor (UF) at a value of 2, as both critical studies used to derive PODs include systemic effects (decreased motor activity).

2. OEHHA recommends an additional UF of 3 be applied to address numerous data gaps in the inhalation toxicity database, and to protect fetuses, infants, and children from the potential developmental neurotoxicity (DNT) of AITC. The inhalation toxicity database is very limited and there are major data gaps in chronic exposure, oncogenicity, reproductive and developmental toxicity, and DNT. In addition, AITC has been shown to be fetotoxic in mice by the oral route, indicating susceptibility to in-utero exposure as well as neurotoxicity (decreased motor activity) in adult animals following both acute and subchronic inhalation exposure. OEHHA therefore is concerned about the potential developmental toxicity effects of the chemical.

C. **Exposure Assessment**

1. There is a need to address data gaps in environmental fate information. Plant materials that release AITC and related isothiocyanates have been studied for decades as alternatives to chemical fumigants. However, soil fumigation with highly-purified AITC is a relatively new pest control approach. Consequently, the environmental fate data available for purified AITC are limited and most studies were performed under laboratory conditions (Borek et al., 1995; Pechacek et al., 1997). This lack of environmental fate data, such as degradation chemicals and soil half-life estimated from field studies, contributes substantially to the overall uncertainties in the AITC exposure estimates and potential health impacts. OEHHA suggests that DPR include an environmental fate section in the document, identify existing data gaps and discuss how this may limit the assessment.

2. Greater transparency in data selection and clarity in statistics used would be useful. Because AITC has limited human exposure and field emission studies, DPR used data from various studies of surrogate chemicals to evaluate occupational and non-occupational exposures. Given the situation, OEHHA agrees with DPR's general approach of using data of surrogate chemicals. However, the reasons for selecting certain soil emission data and the rationale for applying certain statistics to summarize occupational and non-occupational exposures were not clearly stated in the draft EAD.. OEHHA suggests that DPR clearly discuss and quantify if possible how (i) variation within the selected data of surrogate chemicals, and (ii) uncertainties of using surrogate data would impact the AITC exposure estimations.

3. Only inhalation exposures were evaluated and the draft EAD did not include dermal exposure to AITC. AITC is a known skin irritant and sensitizer. This

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concern may be particularly relevant for pesticide handlers who could be dermally exposed to highly concentrated (e.g., >96%) AITC soil fumigant products. AITC residues in soil could also affect post-application workers with limited or no PPE. OEHHA suggests DPR investigate this route of exposure.

II. DETAILED COMMENTS

Our comments on the draft RCD for AITC are grouped into A) Toxicity Evaluation and Risk Assessment and B) Exposure Assessment.

A. Toxicity Evaluation and Risk Assessment

1. Non-cancer Toxicity Evaluation and Point of Departure Determination

a. Pharmacokinetics

The absorption, distribution, metabolism, and excretion of AITC are adequately addressed in the draft RCD. A lack of inhalation absorption data led DPR to assume a default inhalation absorption of 100%. OEHHA notes that the increased levels in urinary bladder tissue in male rats occurs following both oral and intravenous exposure (Ioannou et al., 1984). This study also observed nearly twice the volume of urine in female rats relative to males. Lower urine volume in male rats may have led to more concentrated levels of AITC in the urine and thus in the bladder tissue. However, a previous study by Muztar et al. (1979) observed a two-fold increase in urinary output in male rats administered AITC, compared to controls. Thus, the effect of urinary volumes on AITC disposition is unclear.

There is no data regarding the possibility and extent of pulmonary metabolism of AITC in rodents and humans following inhalation exposure. However, there is also no available data to indicate that the metabolites of AITC through the inhalation and oral routes, at least qualitatively, are expected to be different. As the main route of excretion following oral or intravenous exposure appears to be via urine, it seems likely that increased levels of AITC metabolites in urinary bladder tissue could result from inhalation exposure as well, though there may be quantitative differences depending on the route. Urinary bladder hyperplasia was the critical effect observed in male and female rats following oral exposure, with bladder tumors also observed in male rats.

b. Acute Toxicity

DPR selected a critical acute POD of 2.5 ppm based on decreased motor activity in rats following a single four-hour nose-only exposure to AITC vapor (Herberth et al, 2017). OEHHA agrees that the Herbeth et al. (2017) study is the most sensitive data set available and concurs with the use of a 10-fold LOAEL-to-NOAEL extrapolation factor.

It should be noted that AITC was found to be a dermal sensitizer in studies in humans and mice, and is a respiratory irritant. There is potential for AITC to also be a respiratory sensitizer in humans following repeated exposures.

c. Subchronic Toxicity

A single subchronic inhalation study was identified by DPR. In this 90-day neurotoxicity study, rats were exposed to AITC vapor via whole body inhalation exposure (Randazzo et al, 2017). Squamous cell metaplasia of the respiratory epithelium was observed in a single male rat at the lowest dose tested, 5 ppm, along with degeneration of the olfactory epithelium in a single female rat. The incidence of these histopathological findings increased with dose. A dose dependent decrease in motor activity was also observed in this study, although it only reached significance at 25 ppm. A non-significant decrease of 21-45% in motor activity was observed at 10 ppm, as described in the draft RCD. Based on these neurotoxic effects, along with the histopathological changes observed at 10 ppm, OEHHA agrees with DPR's assessment of a study NOAEL of 5 ppm and LOAEL of 10 ppm.

Several oral subchronic studies were identified and evaluated in both rat and mouse in the draft RCD. Several endpoints were seen in these studies, including decreased body weights, thickened epithelium and hyperplasia of the stomach mucosal lining, and increased liver weight and adrenal weights.

The Hasamura et al. (2011) study reported simple hyperplasia of the urinary bladder in both male and female rats, following 13 weeks of exposure via drinking water (Table 1).

Table 1. Incidence of simple hyperplasia in urinary bladder of rats treated with horseradish extract (HRE) in drinking water for 13 weeks (Hasamura et al., 2011).

	Dose (mg/kg-day)[a]			
	0	10.7	16.3	30.6
Male Rat	0/10	2/10	3/10	10/10**
	0	9.1	17.2	30.7
Female Rat	0/10	1/10	6/10**	10/10**

[a] As reported by study authors; **: p<0.01.

Using the data reported by Hasamura et al (2011), the draft RCD (page 53) determined an oral NOAEL of 6.6 mg/kg-day (it is estimated that 9.1 mg of HRE/kg-day is equivalent to 6.6 mg AITC/kg-day), extrapolated the dose for inhalation exposure, and estimated an equivalent air concentration of 9.5 ppm. It then compared this concentration to the 5 ppm POD derived from the subchronic inhalation study (Randazzo et al., 2017) and asserted that their choice of the inhalation POD is health protective.

OEHHA used the benchmark dose model (BMD) to estimate the PODs of the dataset presented in Table 1 and found some models predict BMDLs lower than the NOAEL of 6.6 mg/kg-day. OEHHA suggests DPR model the data and select the most health protective estimate, after taking into account route-specific issues (e.g., toxicokinetics).

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On page 53 of the draft RCD, DPR also reasoned that because urinary bladder hyperplasia were not observed in the inhalation rat study reported by Randazzo et al. (2017), even in the high-dose rats at 25 ppm, this effect appeared to be specific to the oral route of exposure. OEHHA disagrees that hyperplasia and tumor formation in the urinary bladder are unique to oral expsoure:

1) There is no absorption, distribution, metabolism, and excretion (ADME) data to suggest that different metabolites of AITC are formed following inhalation than with oral exposures, though they may be quantitatively different. Furthermore, the assumption of 100% absorption by inhalation also suggests that exhalation of unchanged AITC is not expected to be significant, and most of the AITC inhaled would be absorbed into systemic circulation. As there is no data indicating an alternative route of excretion, it can only be assumed that these metabolites are mainly excreted through the urine. High concentrations of one or more of these metabolites in the urinary bladder could be expected to cause hyperplasia in this target organ via either route.

2) The fact that no urinary bladder hyperplasia was reported in the 13-week inhalation study (Randazzo et al., 2017) could be explained by either the relatively low exposure levels or the short exposure duration or a combination of both. The study results of Randazzo et al (2017) cannot conclusively prove the effects observed in the subchronic oral studies are not relevant for inhalation exposure. OEHHA recommends DPR to consider the factors discussed in their evaluation of the subchronic oral studies.

d. Chronic toxicity

No inhalation studies for chronic toxicity were available for evaluation in the draft RCD. Two high quality chronic oral toxicity studies are available and were evaluated by DPR: a study in rat and mice using oral gavage (NTP, 1982), and a study in rat using drinking water (Cho et al., 2017). Both studies found evidence of urinary bladder lesions (i.e., hyperplasia and tumors) in male rats.

The POD chosen by DPR for chronic inhalation exposure was 0.5 ppm. For comparison, the lowest chronic oral PODs are 0.6 mg/kg-day ($BMDL_{10}$ for simple urinary bladder hyperplasia in male rats from Cho et al., 2017), and 0.86 mg/kg-day (the LOAEL from NTP (1982) after applying a 10-fold LOAEL-to-NOAEL extrapolation factor). When converted to an internal dose using the conversion metrics listed in the draft RCD in Section D.1.2 on page 54, they are equivalent to 0.9 ppm and 1.25 ppm, respectively, both of which are supportive of DPR's chosen POD, and appear to be protective of urinary bladder effects.

It should be noted that though transitional cell papillomas and epithelial hyperplasia of the urinary bladder were observed in male rats (NTP, 1982), NTP noted that these effects did not occur in the same animals. This would suggest that hyperplasia may not be a required precursor for the urinary bladder tumors, which is contradictory to the statement on pages 55 and 56 in the draft RCD. This will be discussed in greater detail in the Carcinogenicity Section below.

e. Reproductive and Developmental Exposure

Teratology studies were available in mice, rats, hamsters, and rabbits (Morgareidge, 1973). In mice, increased fetal resorptions and fetal death were observed at 28 mg/kg-day, with a developmental NOAEL of 6 mg/kg-day. There were no maternal or developmental effects observed for rabbits or rats.

For the hamster, the draft RCD (page 56) reported an increase in incidence of incomplete sternebral ossification in fetuses of hamsters at the highest tested dose (23.3 mg/kg-day), but stated the effect was not found to be statistically significant or toxicologically relevant. However, in the Summary of Toxicological Data on AITC (2018), DPR reported the increased litter and fetal incidence of incomplete ossification of sternebrae and determined a developmental NOAEL of 5.1 mg/kg-day. OEHHA suggests that DPR address their inconsistencies in the interpretation of the data.

OEHHA disagrees with DPR's determination that fetal and pup effects were plausibly secondary to maternal toxicity and were thus not considered toxicologically significant. Co-occurrence of fetal and maternal toxicity does not necessarily indicate causation. Even if there are sufficient mechanistic data to determine that a fetal effect is due to a specific maternal deficit, the fetal effect still represents developmental toxicity. The US Environmental Protection Agency (US EPA) notes that whether developmental effects are secondary to maternal toxicity or not, the maternal effects may be reversible while effects on the offspring may be permanent (US EPA, 1991).

OEHHA estimated a developmental NOAEL of 6 mg/kg-day (8.7 ppm dose equivalent by inhalation) for fetal resorption and fetal death in the mouse study. Based on the information in the Summary of Toxicological Data on AITC (2018), a NOAEL of 5.1 mg/kg-day (7.4 ppm dose equivalent by inhalation) may also be identified for delayed ossificiation in the hamster (Morgareidge, 1973). The PODs selected in the draft RCD were 2.5 ppm for acute, 5 ppm for subchronic, and 0.5 ppm for chronic exposure. These PODs appear to be protective of reproductive and developmental effects observed in the animal toxicity studies, and OEHHA suggests DPR include dose equivalent calculations for the most sensitive developmental endpoint in their discussion.

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2. Carcinogenicity

The available carcinogenicity studies are two-year gavage studies of food-grade AITC (purity > 93%) in male and female F344/N rats and B6C3F1 mice (NTP, 1982) and two-year drinking water studies of horseradish extract (HRE) containing 82-86% AITC in male and female F344/DuCrj rats (Cho et al., 2017). The draft RCD summarized the three tumor sites (urinary bladder tumors, leukemia, and fibrosarcomas) observed in oral studies. It is OEHHA's position that the three tumor sites are treatment related, and the cancer potency should be based on the multisite analysis for the bladder papilloma and leukemia from the NTP (1982) male rat study.

In the two-year gavage study in male rats, NTP (1982) exposed rats to 12 or 25 mg/kg-day for 103 weeks, and multiple treatment-related tumor types were observed. There were increases in subcutaneous fibrosarcomas in female rats (0/50, 0/50, 3/50) by trend; while this tumor site is treatment-related, it is not the most sensitive for cancer dose response. With regards to undifferentiated leukemia in male rats, OEHHA does not agree with the conclusion in the draft RCD that relies on comparison of leukemia incidence with the historical controls, and suggests including this treatment-related tumor site in the cancer potency estimate. The incidences were 2/50, 6/50, 8/50, or 4%, 12%, and 16%, in control, low-dose, and high-dose, respectively. The incidence in the high-dose group was significantly increased by pairwise comparison with control, and there was a dose-related trend (draft RCD Table 11). NTP (1982) reported that the increase was not statistically significant from the historical controls (96/999 or 10%). However, the NTP (2015) Handbook for Preparing Report on Carcinogen Monographs states that while historical control data from the testing laboratory can be helpful, "the concurrent controls are considered to be the most relevant comparison group for evaluating potential exposure-related tumor effects." As a generally accepted scientific principle, this approach is also used by the US EPA (2005) in its Guidelines for Carcinogen Risk Assessment, which states that the preferred standard for determining statistical significance of tumor incidence comes from a comparison of tumors in dosed animals with those in concurrent control animals. OEHHA also does not agree with the statement in draft RCD that "there was compelling evidence that the observations were artifacts of the study design and the selected rat strain (F344/N) rather than AITC treatment." The undifferentiated leukemia in rats is also known as mononuclear cell leukemia (MNCL) (NTP, 1982). Although OEHHA doesn't assume or require tissue concordance between tumors found in animals studies and those that occur in humans, rat MNCL does have a human counterpart and there is human relevance. US EPA (2012a) noted that several authors have concluded that rat MNCL is similar to human natural killer cell (NK)-large granular lymphocyte leukemia (Stromberg et al., 1985; Ishmael and Dugard, 2006; Thomas et al., 2007). MNCL was also one of the tumor types in the same strain of rat (F344) used by OEHHA to derive a cancer potency

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estimate for Diisononyl Phthalate in the development of a No Significant Risk Level (NSRL) under California's Proposition 65 (OEHHA, 2015).

Increases in urinary bladder transitional-cell papilloma were also observed in the high dose group (0/49, 2/49, 4/49) by trend in male rats (NTP, 1982). Female rats from the NTP study only had one bladder tumor in the high dose group (0/50, 0/50, 1/50). In Table 11 of the draft RCD, there is a mistake indicating significance by pairwise comparison in the high dose males, when the p value is in fact not statistically significant. There was also a typo in the table legend indicating statistical significance at p<0.5, rather than p<0.05. However, when calculating animals at risk, OEHHA suggests using animals alive at the appearance of the first tumor. There was an approximate 25% mortality in the high dose group at the appearance of the first bladder tumor. When analyzing tumor incidences with animals at risk as the sample size, the incidence of transitional-cell papilloma in the high dose males was statistically significant by pair-wise comparison. OEHHA recommends DPR reevaluate incidences of all tumors using this method. In the two-year drinking water study by Cho et al (2017), there were also increases in urinary bladder papilloma in high-dose male rats (1/32, 0/32, 3/32), but the incidences were not statistically significant by pairwise or by Exact trend test. Regardless, urinary bladder transitional-cell papilloma is a rare tumor type (Haseman et al. 1998) and OEHHA considers the urinary bladder transitional-cell papilloma to be treatment-related with the data from male rats in the NTP study (1982) adequate for cancer potency estimation. Furthermore, OEHHA does not see evidence that these tumors were caused by route-specific mechanisms. AITC has not been adequately tested by inhalation in two-year cancer bioassays, and it is inappropriate to make conclusions for the inhalation route based on results from sub-chronic studies. There is no evidence for route-specific differences in ADME that supports the hypothesis that the the carcinogenic effect of AITC is limited to the oral route. The draft RCD noted in the ADME section that "The oral absorption in rats and mice was estimated to be > 90%. DPR considers oral absorption > 90% as complete (100%). In the absence of data for inhalation uptake, DPR assumes a default inhalation absorption of 100%." In addition, positive findings related to some cancer key characteristics (electrophilicity, genotoxicity and induction of oxidative stress) indicate that AITC acts systemically. This is discussed below.

The draft RCD does not cite some positive genotoxicity studies cited in IARC (1999). We have listed the omitted studies in the Minor Comments section for DPR's consideration.   OEHHA disagrees with the conclusion in the draft RCD that "any positive results for AITC may not have been mediated by direct DNA-reactivity." AITC is a highly reactive compound, which has been shown in vitro to form adducts with proteins (Kawakishi & Kaneko, 1987) and glutathione (Kawakishi & Kaneko, 1985). A study by Kassie and Knasmuller (2000) found that AITC induced formation of thiobarbituric acid reactive substances (a marker of lipid peroxidation) in HepG2 cells *in*

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vitro, and that reactive oxygen species may be involved in the AITC induced DNA damage in *E coli*. These findings are related to electrophilicity and induction of oxidative stress, two key characteristics of carcinogens (Guyton et al., 2018). Positive results of several genotoxic endpoints as summarized in the draft RCD and by IARC (1999) support that AITC is genotoxic to various cellular targets in vitro, and/or in vivo. Notably, AITC induced DNA strand breaks and oxidative damage to DNA in humans *in vivo* (Charron et al. 2013). While there are negative and some weakly positive or equivocal findings in the genotoxicity database, it is OEHHA's opinion that they are not sufficient to discount the positive genotoxicity findings.

Based on consideration of all the information available, the default approach is to apply a linearized multistage model to derive a cancer potency estimate for each tumor site. For carcinogens that induce tumors at multiple sites in a particular species and sex, US EPA's Benchmark Dose Software (BMDS) can be used to derive maximum likelihood estimates (MLEs) for the parameters of the multisite carcinogenicity model by summing the MLEs for the individual multistage models from the different sites and/or cell types. This multisite model provides a basis for estimating the cumulative risk of carcinogen treatment-related tumors.

3. Extrapolation, Variability, and Uncertainty

a. Interspecies Extrapolation and RGDR Approach

To convert inhalation doses from animal studies to Human Equivalent Concentrations (HEC)[1], OEHHA supports DPR's use of the RGDR methodology developed by US EPA for non-cancer adverse effects (US EPA, 1994). When the adverse effect is the result of systemic metabolism and distribution, the assumption is that the difference in breathing rates and surface areas between humans and the animal model is not important, because the distribution of the chemical between the blood and the air in the lung reaches equilibrium. Thus, the default RGDR is a value of 1, based on the assumed same blood:air partition coefficients for humans and animals. When the adverse effects are in the respiratory tract and considered portal of entry effects, it is assumed that the locally absorbed dose is the critical dose metric and is a function of

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[1] The equation for HEC is:
HEC = POD x (formulation purity) x (Da / Dh) x (Wa / Wh) x RGDR, with a=animal, D=days, h=human, and W=weeks.

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breathing rates and surface area at the site of deposition and absorption. In the draft RCD, DPR assumed a systemic effect for acute exposure (decreased motor activity) and systemic or portal of entry effects for subchronic and chronic exposure (decreased motor activity and histopathological changes in the olfactory epithelium). In all scenarios, a dose adjustment factor of 1 was applied. OEHHA agrees with DPR's assumptions and calculations of HECs, yet has some comments on the UFs used to calculate MOEs.

For the RGDR approach for non-cancer effects, DPR decreased the conventional interspecies UF of 10 to $\sqrt{10}$. This is based on the assumption that the RGDR already accounted for the pharmacokinetic portion of the interspecies factor. OEHHA agrees that if a chemical is causing a portal of entry effect and local metabolism is generally not a concern, the reduction in the pharmacokinetic portion of the UF to a value of 1 is appropriate. However, when the critical effect is systemic in nature, and may involve metabolism, a UF for interspecies pharmacokinetics should be retained with a value of 2 to account for potential uncertainty (OEHHA, 2008). This is especially warranted for AITC due to the absence of pharmacokinetic data following inhalation exposure, and the concern for effects seen in the urinary bladder following oral exposure which are attributed to excretion of AITC-metabolites. Thus, this interspecies UF_K of 2 should be considered for all durations of exposure, as the critical effects are considered systemic effects. The total interspecies UF would then be 6, not 3 (rounded).

   b. Intraspecies Extrapolation

In the draft RCD, a default UF of 10-fold was applied to account for intraspecies variability within the human population (UF_H). This is generally considered to be a factor of $\sqrt{10}$ for pharmacokinetics and $\sqrt{10}$ for pharmacodynamics. It is OEHHA's opinion that an intraspecies UF of 10 is insufficient as there are many factors affecting human variability in response to a chemical exposure (OEHHA, 2008; Zeise et al. 2013). The scientific basis for this recommendation is detailed in OEHHA's peer reviewed Air Toxics Hot Spots Risk Assessment Guidelines, Technical Support Document for the Derivation of Reference Exposure Levels (OEHHA, 2008). Based on analyses of human pharmacokinetic variability, OEHHA's practice is to increase the traditional intraspecies pharmacokinetic UF of $\sqrt{10}$ to 10. This increase would account for the wide variability in pharmacokinetics in the population, especially among subpopulations such as infants and children, pregnant women, and the elderly. Thus, OEHHA recommends DPR expand their concerns for these subpopulations and increase the intraspecies pharmacokinetic UF to 10, resulting in a total UF_H of 30.

   c. Sensitive Population and Limited Inhalation Toxicity Database

OEHHA recommends an additional UF of $\sqrt{10}$ be applied to address the limited inhalation toxicity database as there are major data gaps in chronic exposure,

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oncogenicity, and reproductive and developmental toxicity by the inhalation route, which is the primary route of human exposure. In addition, there is no DNT data by any route on the potential effects of AITC on the developing brains of fetuses, infants and children. Evidence of neurotoxicity was observed as the primary critical effect in the three inhalation toxicity studies and there is evidence that AITC can impact fetuses as indicated by an oral developmental toxicity study of AITC at doses that, when converted to external air concentrations, were similar to the subchronic inhalation POD (Morgareidge, 1973).

> d. Risk Characterization

The Margin of Exposure (MOE) approach was used to evaluate non-cancer hazards. The draft RCD characterized whether an exposure is likely to cause adverse health effects using a target MOE of 30 for all age groups. OEHHA recommends a target MOE of 600 for all age groups, occupational and non-occupational, to take into account the recommended higher pharmacokinetic portions of the interspecies (2) and intraspecies ($\sqrt{10}$) UF's, and an additional UF ($\sqrt{10}$) to protect potentially sensitive individuals from protential health effects, given the very limited inhalation toxicity database, and to protect fetuses, infants, and children from concern for developmental neurotoxicity.

B. Exposure Assessment

> 1. Environmental Fate of AITC - Degradants

In aqueous solutions, Pechacek et al (1997) demonstrated that 24-50% of AITC was transformed into allylamine and 11-26% was transformed to carbon disulfide. Both chemicals are highly volatile at ambient temperature and pressure. Allylamine could cause eye and respiratory tract irritation. Carbon disulfide is listed as a reproductive toxicant under Proposition 65.

OEHHA suggests that DPR discuss if soil emissions of carbon disulfide, allylamine, or other AITC degradants are possible under field conditions, and if these chemicals, which are not evaluated in the draft EAD, can potentially pose a health hazard to handlers and bystanders.

> 2. Occupational Exposure of On-site Workers

> a. Exposure scenarios

DPR used data from surrogate chemicals and product label to define exposure scenarios. For each application method (shallow shank with and without tarp, deep

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shank with and without tarp and drip) and whenever relevant, DPR estimated exposure for three types of handlers and one type of re-entry workers. Handlers included pesticide loaders, pesticide handlers involved in the application of the fumigant on the field (driver, copilot, tarper, soil sealer) and pesticide handlers involved in the removal of the tarp (tarp-cutter, remover and puncher). Re-entry workers included soil shapers and pipe layers. OEHHA agrees with these scenarios for on-site workers. Off-site workers are discussed in the bystander section below.

b. Surrogate Data

Breathing level air concentrations of MITC (methyl isothiocyanate), a structural analog of AITC, have been measured for some application methods. However, unlike AITC, a precursor chemical (metam sodium or metam potassium) is first applied to the soil and then converts into MITC over the next 2-24 hours. For this reason, DPR stated that MITC studies are less likely to be relevant to AITC applicator exposure scenarios compared to 1,3-D or chloropicrin studies. OEHHA agrees with this assumption and the use of 1,3-D and chloropicrin as surrogate chemicals in estimating occupational exposures for on-site workers.

c. Re-entry Interval

The proposed re-entry interval (REI) is 5 days following application, with or without tarp. Due to limited field data, it has not been demonstrated if all the applied AITC would be depleted after 5 days. In a field data study presented by the registrant, the peak emission rate of AITC when the PE tarp was cut after Day 5 was as high as 80% of the highest peak emission rate observed (Ajwa et al., 2014). This suggests that if a certain set of environmental conditions increases the soil half-life of AITC, a significant percentage of the applied chemical could still be present after 5 days, which could lead to higher than expected soil emission following the expiration of REI.

d. Statistics

Two surrogate fumigant chemicals, 1,3-D and chloropicrin, were used to estimate occupational exposure to AITC. For a given worker exposure scenario, a wide range of breathing zone air concentrations of 1,3-D or chloropicrin were obtained from field studies at different locations, using different application methods, and under different environmental conditions.

DPR reported the 95th percentiles of the exposure data when multiple studies were available. The 95th percentile calculation in the draft EAD (DPR EAD-95th) cited the method introduced in a DPR memo, which is different from the 95th percentile commonly used in statistical analysis (DPR, 2009). The commonly known 95th percentile is a type

of non-parametric summary of the sampling data. The DPR method calculates the mean and standard deviation of the natural logarithms of the sampling data, uses two estimated statistics to determine a hypothetical log normal distribution, and then estimates the 95th percentile of the hypothetical distribution as DPR EAD-95th (DPR, 2009). This method relies on two assumptions: (1) the true exposure data has a log-normal distribution; (2) the measured exposure samples are representative and therefore their statistics can be used to determine the log-normal distribution of the exposure data. DPR EAD-95th can generate a reasonable high-end estimation that usually cannot be achieved from the small sample numbers typically collected in field studies. The draft EAD did not provide the necessary analysis to show these two assumptions were met in the calculation of the DPR EAD-95th for applicators during shank and drip applications (Pages 15 - 20 the draft EAD). OEHHA suggests DPR provide the necessary supporting information for these assumptions.

For each scenario of loader, tarp-cutter, and re-entry workers, the draft EAD only provided one data point, instead of statistics. OEHHA suggests DPR clarify what the nature of the "data point" is (e.g., 77021 µg/m3 in footnote of Table 17, Page 21, Draft EAD; 4117 µg/m3 in footnote of Table 18, Page 22, Draft EAD; and 173 µg/m3 in footnote of Table 19, Page 22, Draft EAD).

  e. Combining data from studies of two different chemicals and two application methods

Data from two surrogate chemicals, chloropicrin and 1,3-D (Table 10, Page 17, draft EAD) or from two different application conditions, drip applications with and without tarp (Table 14, Page 20, draft EAD), were combined to derive summary statistics (i.e. average, standard deviation, DPR EAD-95th, and range) (Table A). This approach may not be justified because of two issues:

1) Datasets from different application methods (e.g., tarped and un-tarped) or chemicals (e.g., chloropicrin and 1,3-D) should not be combined. Their emission rates and emission profiles are likely to be very different.
2) The combined data may not meet the distribution assumption required for the calculation of DPR EAD-95th as described in the previous comment. For example, the average air concentrations of chloropicrin and 1,3-D measured from applicator breathing zones using broadcast and bed shank application (shown in Table 10 of the draft EAD) are 366 $\mu g/m^3$ and 3,238 $\mu g/m^3$, respectively. This suggest the combined dataset of chloropicrin and 1,3-D is likely to have a bimodal distribution, not log-normal.

OEHHA suggests that DPR revise this approach or discuss its limitations.

f.   Uncertainties in estimating the number of AITC exposure days per year

Both 1,3-D and AITC applications are intended to target soil nematodes, so it is reasonable to derive the application days of AITC in a year (same as the worker exposure days in a year) estimates from 1,3-D data. For 1,3-D, the annual worker exposure days estimates are significantly lower in the 2014-2018 period compared to those from the 2010-2014 period and we believe this could be due to the implementation of a ban on December application since 2016. The total annual amount of 1,3-D used actually went up from the 2010-2014 period to the 2014-2018 period. The draft EAD used the 2014-2018 data for deriving estimates of annual worker exposure days for AITC. As of now, AITC usage is not subject to any restrictions and the label allows for more than one application per year. OEHHA is concerned that using the 1,3-D data from the 2014-2018 period may under-estimate workers' annual and lifetime exposures to AITC. Therefore, OEHHA recommends DPR discuss the limitations of the approach used and investigate other approaches to better estimate the workers' exposure days per year.

1. Off-site Workers and Residential Bystanders

a. Exposure scenarios

The product labels for AITC prohibit application within 25 feet of any occupied structure and the registrant's training material recommends no application be done within 100 feet of any sensitive site. Therefore, for each application method, DPR estimated exposure for off-site workers at the field edge and for residential bystanders (children and adults) at 25 and 100 ft from the field edge. OEHHA agrees with these scenarios for off-site workers and residential bystanders.

b. Emission using surrogate data

As shown in Table 11 (Page 56, draft EAD) and reference list, there are various studies of 1,3-D and chloropicrin for some application method. It is unclear how the surrogate numbers in Table E1 (Page 39, draft EAD) were selected from multiple studies. OEHHA recommends that DPR describe how emission rate data were selected and why a particular study was chosen.

c. Peak emission period of shallow shank with tarp

Table E1 (Page 39, draft EAD) listed the "maximum TWA emission" that were used in the AERMOD modeling of AITC bystanders' exposure. Using the listed data, the mass loss (%) during the maximum emission period can be calculated by the following equation for each corresponding scenario.

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$$Mass\ Loss\ (\%) = \frac{emission\ \times\ duration}{application\ rate}$$

Emission data used by DPR was summarized for the first 5 days after application (Page 45-46, Appendix 1). Based on the data used by DPR, shallow shank with tarp was estimated to have maximum 2% daily mass loss due to soil emission in the first 5 days post application; therefore, the total soil emission over 5 days would cause <= 10% mass loss. Assuming AITC degradation half-life in soil is 2.5 days (USDA, 2014; US EPA, 2013), degradation could cause about 75% mass loss over the first 5 days. Considering both degradation and emission of AITC in soil in the first 5 days, 15% of AITC application amount could still be available and be released if tarp cutting occurs on the 6th day. OEHHA recommends that DPR analyze the environmental fate of AITC and evaluate the emission profile for at least 6 days to cover the tarp-cutting period.

     d. Modeling bystander exposure with AERMOD

DPR modeled six 4-hr periods, three 8-hr periods, and one 24-hr period for each day over a 5 year period and used the maximum air concentrations of all modeling periods, all modeled counties, and the 5 years of weather conditions for bystanders' exposure assessment. DPR explained that using the maximums of the 5-year weather data was intended to compensate for the uncertainty in the emission data. However, using weather data for multiple years and multiple locations to characterize various dispersion conditions on the predicted air concentrations cannot compensate for the uncertainty in the emission rates.

Estimation of soil emission and air dispersion are two separate steps needed to predict air concentration and off-site workers and residential bystanders' inhalation exposures. OEHHA recommends DPR carefully evaluate soil emission rates and select the most appropriate dataset(s) and statistics for air dispersion modeling.

     e. Annual and long-term exposure

The seasonal, annual and lifetime doses were not estimated for residential bystanders and off-site workers. Because fumigation of a field may not happen all at once and a worker can work in multiple fields in the same area or across counties, it is possible for an off-site workers to be exposed to AITC many times a year. It is also possible that several AITC applications could occur sequentially near the same location and result in residential bystander exposure that lasts more than a few days. Lastly, the draft EAD notes that the DOMINUS® product can be used for end-of-season post-plant crop termination applications. OEHHA suggests DPR consider including seasonal, annual and lifetime exposure estimates for residential bystanders and off-site workers.

f. Pesticide-related illness

The Isagro AITC products have been used outside of California for several years since US EPA approval in 2014. The Sentinel Event Notification System for Occupational Risk (SENSOR) program at NIOSH may have reports of pesticide illness related to AITC use in the 13 other participating states. OEHHA suggests that DPR consult the SENSOR program at NIOSH and ask if any AITC-related illnesses associated with soil fumigation have been reported in the US.

Secondly, California does have many reports of MITC-related illnesses and injury that were associated with bystander or re-entry worker exposure. MITC is regulated as a toxic air contaminant. Because AITC and MITC share similar chemical structures and many chemical properties as well as some application methods, there is a concern that AITC may pose a similar health hazard. OEHHA recommends that DPR evaluate this possibility in the draft EAD.

III. RESPONSE TO CHARGE STATEMENTS

DPR asked OEHHA to address charge questions in our peer review of the risk assessment. The answers provided in this section are purposely brief with more in-depth discussion of these answers and OEHHA's other comments in Section II, Detailed Comments.

A. Hazard Identification

1) Acute POD: A default 10x LOAEL-to-NOAEL extrapolation factor was used to establish the critical acute POD of 2.5 ppm.

OEHHA agrees with the use of a dose extrapolation factor of 10, as the critical study included neurobehavioral effects at the lowest dose tested. This default factor is typically applied when extrapolating from a LOAEL to a NOAEL.

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.

OEHHA concurs with the use of an extrapolation factor of 10 to extrapolate from subchronic to chronic exposures, as a study with a longer exposure duration is not available. However, OEHHA recommends the most health protective studies for each exposure duration are used to derive PODs, after taking into account ADME differences. OEHHA suggests DPR use BMD or other appropriate dose-response evaluation methods to confirm that the most health protective POD is selected from the available inhalation and oral toxicity studies.

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

While oral toxicity studies were evaluated in the draft RCD and were used to satisfy data requirements to support registration, only inhalation studies were considered when evaluating critical effects and PODs. OEHHA finds this approach problematic. Critical effects identified in the oral toxicity studies were dismissed over "concerns about route specificity of observed effects," yet the inhalation studies available are too limited to adequately characterize chronic, reproductive, or developmental effects resulting from inhalation exposure.

Urinary bladder hyperplasia was a common adverse effect in rats following oral exposure to AITC for various exposure durations, including a two-generation reproductive and developmental study. The draft RCD attributed the development

of urinary bladder hyperplasia to sustained high levels of AITC-metabolites in urine (section E.1.7, draft RCD). Because urinary bladder hyperplasia was not found in a single subchronic inhalation study, DPR determined that bladder effects were specific to the oral route. While detailed ADME data following inhalation exposure are not available, it is clear that both oral and IV administration lead to increased AITC-metabolite levels in bladder tissues, particularly in male rats. There is no data on first pass metabolism by the lung, nor data to suggest that the expected route of excretion of AITC metabolites following inhalation is different than following oral exposure. The fact that no urinary bladder hyperplasia was reported in the 13-week inhalation study (Randazzo et al., 2017) could be explained by either the relatively low exposure levels or the short exposure duration or a combination of both. Thus, OEHHA disagrees that urinary bladder effects are specific to the oral route and are irrelevant to the inhalation route.

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

The available chronic toxicity/carcinogenicity studies indicate that AITC is an animal carcinogen, and this determination is supported by the induction of urinary bladder tumors, leukemia, and fibrosarcoma in rat oral studies. AITC is a highly reactive compound and can react with protein and DNA in vitro through adduct formation or generation of reactive oxygen species. OEHHA also determined AITC to be genotoxic; this is supported by several positive genotoxic endpoints as summarized in the draft RCD and by IARC (1999). Additional information is provided in the detailed comments. OEHHA suggests DPR quantitatively estimate cancer risk of AITC in its risk assessment.

B. 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.**

In this exposure assessment, DPR used breathing-level air concentrations measured in multiple chloropicrin or 1,3-D field studies to estimate inhalation exposure for a variety of occupational exposure scenarios. DPR did not use MITC as a surrogate chemical in the draft EAD because there was insufficient worker exposure data for all scenarios and MITC must form after the precursor chemical has been applied. Based on a comparison of vapor pressure, molecular weight, water solubility and octanol-water partition coefficients, AITC exposure estimates are likely to be less than the exposure estimates obtained from surrogate fumigants under similar environmental conditions. Perhaps most importantly, the vapor

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pressure of AITC is 6.7 to 9.2-fold lower than the vapor pressure of 1,3-D and chloropicrin (Table 1, page 4, draft EAD).

OEHHA verified all of the AITC dose calculations for occupational exposures, but has not verified that the breathing-level air concentrations from the 1,3-D and chloropicrin were correctly reported from the registrant studies. OEHHA agrees that, in general, these estimates are reasonable and health-protective. However, OEHHA has some concerns about certain instances where disparate datasets were pooled. For example, Table 14 (page 20, draft EAD) shows that use of PE tarps reduced average breathing zone air concentrations by 44% (6 applicators) compared to un-tarped applications (6 applicators). The pooled-value exposure concentration is lower than if the un-tarped value were calculated separately. OEHHA recommends that exposure estimates from tarped and un-tarped applications be calculated separately so that the exposure from un-tarped applications will not be underestimated.

The draft EAD did not discuss environmental fate processes (soil dissipation, adsorption, chemical reactivity with soil constituents and aqueous-phase degradation) that reduce AITC levels in soil and ultimately impact the amount of AITC soil emissions. Laboratory studies reveal that the soil half-life of AITC can vary 3-fold due to factors such as soil type, temperature, pH and moisture levels (Borek et al., 1995). A longer soil half-life (60+ hours) would result in higher than expected emissions during and shortly after tarp cutting. In addition, high levels of soil residues could potentially cause dermal exposure of re-entry workers (soil shapers and pipe layers) who are not required to use any personal protective equipment (PPE) following expiration of the 5-day REI. We note that the Dominus product label suggests that growers test AITC-treated soil for phytotoxic residues "after a minimum of 7 days after application".

OEHHA suggests DPR expand the environmental fate discussion in the RCD including how variation in environmental conditions may affect emission rate at the time of tarp cutting and influence inhalation exposure of workers and nearby residents.

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.**

DPR used the AERMOD model to estimate inhalation exposure for occupational bystanders (i.e., off-site workers) at the field edge and for residential bystanders (children and adults) at 25 and 100 ft from the field edge. This approach is consistent with both the product label (25 feet from occupied structure) and the registrant's training material (100 feet from sensitive sites). OEHHA agrees with DPR's choice of an AERMOD-based modeling approach to estimate off-field air concentrations. OEHHA verified the dose estimate calculations used for the bystander scenarios, but did not reproduce AERMOD estimates for air concentrations.

Specific surrogate-chemical studies and emission rate values were used to estimate bystander exposures of some application methods when AITC specific data were not available. OEHHA believes this approach is reasonable given the lack of AITC emission data for some application methods. Furthermore, DPR applied a similar approach in the 1,3-D risk assessment to estimate exposure in previous exposure assessments (DPR, 2015).

However, the draft EAD did not describe the data selection process. OEHHA suggests that DPR provide reasons and justifications for selecting the specific surrogate chemical studies to estimate emission rates in some bystander exposure scenarios.

Recently DPR used the HYDRUS model to estimate 1,3-D soil emissions when developing mitigation measures for all the application methods of 1,3-D. Since AITC field data are limited, OEHHA suggests DPR consider a similar approach or at least compare HYDRUS-derived results with available AITC field studies to evaluate this approach in AITC exposure assessment.

C. 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).

OEHHA supports the use of the RGDR approach to convert doses in animal inhalation experiments to human equivalent concentrations (HEC) for non-cancer effects. However, for effects that are systemic in nature, it is OEHHA's position that the RGDR approach does not account for interspecies differences in metabolism or excretion (see additional discussion in detailed comments). Therefore, OEHHA

recommends retaining an interspecies pharmacokinetic UF of 2, resulting in a total interspecies UF of 6, rather than 3 as presented in the draft RCD.

D. Worker and Bystander MOEs

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

OEHHA agrees with the chosen durations to estimate occupational risks of on-site workers in the draft RCD, and noted that many occupational exposure scenarios are far below DPR's target MOE of 30. As noted in the Risk Characterization section, OEHHA suggests a target MOE of 600.

9) Risk to off-site workers and residential bystanders, were estimated for acute exposures.

Based on the proposed uses of AITC and its toxicological properties, OEHHA recommends estimates for seasonal, annual, and lifetime exposures of off-site workers and residential bystanders be included in the assessment. It is of concern to OEHHA that all the acute exposure scenarios for off-site workers and residential bystanders, including children, were below the draft RCD's target MOE of 30, and would be well below OEHHA's suggested target MOE of 600.

IV. MINOR COMMENTS

A. Draft RCD

Table 5 on page 28: body weight percent change for females at 25 ppm is incorrect; it should be 12% rather than 125%.

Notation for Table 6 does not match the footnotes of the table. There are mixed letters and numbers contained in the table, but only letters are listed in the footnotes.

Reference at the top of page 31 for Lewerenz et al, 1988a is incorrect. Decreased total cholesterol was observed in Hasamura et al, 2011.

The Estimated AITC Dose in mg/kg-day differs between Tables 12 and 13. Table 12 shows the calculated AITC intake whereas Table 13 lists the estimated HRE intake. Values for Table 13 Estimated AITC Dose (mg/kg-day) should be 0, 2.2, 4.4, and 16.8, assuming 82% AITC content in the HRE used (as assumed when calculating estimated AITC dose in Table 12).

Regarding the genotoxicity evidence, the draft RCD did not include some positive studies summarized by IARC (1999). OEHHA suggests including the following in the genotoxicity section.

- Reverse mutation in *Escherichia coli* WP67 (Rihová, 1982, as cited in IARC, 1999);
- Chromosomal aberrations in *Allium cepa* (Sharma and Sharma, 1962, as cited in IARC, 1999);
- Drosophila melanogaster sex-linked recessive lethal mutations (Auerbach and Robson, 1944 and 1947, as cited in IARC, 1999);
- The summary for Tripathi et al. (2015, as cited in the draft RCD) is missing the induction of gamma-H2AX, a marker for DNA damage and/or double-strand breaks.

B. Draft EAD

1. Definition of Buffer Zone

The buffer zone defined in this document refers to what is known as a setback, which is the distance between a treated field and any occupied structure. However, the most commonly recognized definition of buffer zone is a distance between the application site (i.e., edge of field) and any bystander, residential or occupational. Therefore, as mentioned in the US EPA factsheet on buffer zones, "all non-handlers including field workers, nearby residents, pedestrians, and other bystanders must be excluded from

the buffer zone during the buffer zone period, except for people in transit" (US EPA, 2012b).

OEHHA believes the use of the term buffer zone in this document is misleading and should be consistent with the way DPR uses this term when doing mitigations.

2. There are inconsistencies in the Maximum TWA emission values for AITC shank applications presented in:

- Table 26 (page 30, draft EAD) – Typo – Emission rates for AITC (shallow shank) should be consistent with other values in these documents
- Table E1 (page 39, Appendix 1, draft EAD), Table 9 (page 52, Appendix 1, draft EAD), and Table 11 (page 56-57, Appendix 1, draft EAD) appear to be correct, however it would be more informative to consistently indicate TIF or PE tarp instead of study field number (Table D).

Table D: Maximum TWA Emission (µg/m^2/s) for AITC Shallow/Broadcast Shank

	4 hr TWA	8 hr TWA	24 hr TWA	Comment
Table 26 (page 30)	12.6	8.4	17.8	Labeled as PE
Table E1 (page 39)	17.8	12.6	8.4	Labeled as "w tarp"
Table 9 (page 52)	17.8	12.6	8.4	Labeled as Field 4
Table 11 (page 56-57)	17.8	12.6	8.4	Labeled as PE

OEHHA suggests that DPR revise the main draft EAD document so that those values match up with the values in the supporting documents and that Table 9 in Appendix 1 be revised for clarity.

3. There are inconsistencies in the application rate and maximum TWA emission values for AITC Drip application. OEHHA suggests that DPR review and revise all the numbers as necessary.
- The concentrations of drip application were generally normalized to the rate of 246 lbs/ac in the draft EAD; but several places in the Appendix used 245 lbs/ac (Table E1, Page 39; Table 9 – 10, Page 52-53; Figure 4, Page 54).

- In Table 5 (page 46, Appendix 1, draft EAD) and Table 11 (pages 56-57, Appendix 1, draft EAD), the maximum TWA emissions for drip application values were normalized to an application rate of 340 lbs/acre.

- As shown in Table E, the maximum TWA emissions values vary from table to table for drip application. The values in table 11 are about 40% higher than the other tables.

- Also, please provide consistent tarp and treatment information instead of field number.

Table E: Maximum TWA Emission (µg/m^2/s) for AITC Drip with Tarp

	Max 4 hr TWA	Max 8 hr TWA	Max 24 hr TWA	Comment
Table 26 (page 30, Draft EAD)	99.5	79.9	53.5	Labeled as PE
Table E1 (page 39, Appendix 1)	99.3	79.7	53.4	Labeled as "w tarp"
Table 9 (page 52, Appendix 1)	46.7	40.8	13.8	Labeled as Field 1
	99.3	79.7	53.4	Labeled as Field 3
Table 11 (page 56-57, Appendix 1)	64.6	56.5	19.1	Labeled as TIF
	137.5	110.4	73.9	Labeled as PE

3. The draft EAD listed Oakland as the upper air station for the modeling site at Siskiyou County, which is not the appropriate air station for this location (Table 2, Page 70, draft EAD). The correct upper air station for Siskiyou County should be KMFR at Medford, OR.

4. Figure 3 (Page 49, draft EAD) – These 4 graphs show MITC emission rates under a variety of conditions (shank, drip and 3 tarp options). However, the graphs are not labeled to clearly show which conditions apply to each, so the information cannot not be easily compared to the AITC study data.

5. Typos in Page 29-30. (Appraisal B, draft EAD):

- Page 29, last line – typo – should be "AITC" instead of MITC,
- Page 30, line 4 – typo – should be "Table 26" instead of Table 27

VI.   REFERENCES

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