



MEMORANDUM

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Department of Pesticide Regulation
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DATE: May 25, 2020

SUBJECT: Response to comments by Dr. Chensheng (Alex) Lu on DPR's draft Addendum to the 2006 Sulfuryl Fluoride Risk Characterization Document dated December 2018

I. Background

The Department of Pesticide Regulation (DPR) requested external scientific review of its draft Addendum to the 2006 Sulfuryl Fluoride Risk Characterization Document according to the 2006 California Environmental Protection Agency External Scientific Peer Review Guidelines. Dr. Chensheng (Alex) Lu of the College of Resources and Environment of Southwest University in Chongqing, China was one of the assigned reviewers asked to comment on the main assumptions and conclusions of the draft Addendum (see Appendix A). We sincerely appreciate the time and effort Dr. Lu spent in thoroughly reviewing and commenting on the draft Addendum and two of the main conclusions (#1, #4). This memorandum is in response to those comments. The final Addendum referenced throughout this response refers to DPR's final May 2020 Addendum to the Sulfuryl Fluoride Risk Characterization Document.

II. Response to Comments

Conclusion 1 – *The scientific basis for the proposed RfCs depend both on the nature of the observed effects (non-neurotoxic vs. neurotoxic) and on the assumed mode of action (systemic vs. portal of entry).*

Dr. C. Lu, comment 1: Reviewer wants to acknowledge DPR's thorough preparation of this Addendum. The scientific basis for the proposed RfCs depend both on the nature of the observed effects (non-neurotoxic vs. neurotoxic) and on the assumed mode of action (systemic

vs. portal of entry) was sound, and the Reviewer has no further comment on the RfC derivations.

DPR response: No response necessary.

Lu, comment 2: As summarized in the Addendum, the respiratory effects were almost always observed at the same doses as those causing neurotoxic effects, suggesting that SF could produce both systemic and portal of entry effects at the same doses. Since brain has been identified as the most sensitive target tissue for SF and the incidence and severity of brain damage depended upon the degree of SF exposure, and the respiratory effects were almost always observed at the same doses as those causing neurotoxic effects, it is very difficult to argue that SF should be classified as having either systemic or portal of entry effects. In fact, those data indirectly suggested that SF could have systemic and portal of entry effects simultaneously. This makes sense because once SF is inhaled some of SF will be retained at the portal of entry and the remaining will be distributed systemically. Therefore, it is the Reviewer's opinion that the traditional methodology for HEC calculation should be applicable to SF with both the systemic effects through blood circulation AND portal of entry effects at the respiratory tract.

DPR response: DPR agrees with Dr. Lu's comment that sulfuranyl fluoride could have systemic and portal of entry effects simultaneously, and has incorporated this comment in Appendix E.

“Alternatively, it is possible that all of the pathways described above – olfactory/trigeminal, local vascular, and the systemic circulatory – comprise brain entry routes and thus collectively contribute to the lesions associated with sulfuranyl fluoride exposure.”

Lu, comment 3: Nevertheless, the Reviewer is convinced that the current RfC derivations that DPR presented in this Addendum may not address the real effects thru a MOA that DPR is acknowledged but has not incorporated in this Addendum. In the Conclusion of this Addendum, DPR stated and agreed that assessments conducted by all international agencies recognized fluoride is the active principal in the toxicity of sulfuranyl fluoride in which it exerts its effects through a systemic mode of action (MOA). However, DPR also concluded that available data might not support a conventional systemic MOA for neurotoxicity that results following inhalation exposure. The suggestive direct pathway for fluoride entering brain thru the intranasal cavity, as described in the Appendix E, is critical because brain has been identified as the most sensitive target tissue for SF and the incidence and severity of brain damage depended upon the degree of SF exposure. This is also true that once brain is damaged at the pre- and postnatal development periods, those damages are likely irreversible.

DPR response: See our response to **Lu comment 5** below.

Lu, comment 4: Although exactly how fluoride could enter brain region thru the intranasal route remains unknown, data for other chemicals has proven such entry route plausible and valid. Data shown in Figure 1 in Appendix E provided the valid support of the intranasal entry to the brain region for SF. The T/P ratios resulting from inhalation exposure to SF stand out in the upper right-hand corner of the graph, which clearly demonstrates an influx of SF (or fluoride) entering brain region post-inhalation route of exposure in rats not *via* blood-brain-barrier. If the intranasal entry route does occur, the most important question is how much of SF will take this intranasal entry route. From the data shown in Figure 1 in Appendix E, it does look like a significant amount of SF would take the intranasal entry route, or it would not lead to T/P ratios higher than 1.

DPR response: No response necessary.

Lu, comment 5: After thoroughly reviewing the Addendum, it is Reviewer's opinion that DPR shall only establish one RfC for the MOA of intranasal route of neurotoxicity for sulfuryl fluoride (SF) for the following reasons. By leaving this significant MOA and the health effects in brain out of the regulatory consideration would not bring this Addendum to be in accordance to the updated toxicological information for SF.

DPR response: DPR appreciates Dr. Lu's concurrence regarding the potential for direct intranasal access of fluoride (or other toxic species) to brain. The neurological effects of sulfuryl fluoride may result from multiple routes of entry, including intranasal, local vascular, and systemic (see revised Appendix E in the final Addendum). Without definitive proof, DPR cannot establish the reference concentration (RfC) solely on the intranasal route mode of action (MOA). Nonetheless, DPR recognized the potential effect of this significant MOA, as RfCs were calculated based on different MOA assumptions (systemic, portal of entry, or unknown MOA) (see Summary Table 1 in the final Addendum).

Conclusion 4 – UFs used to calculate RfCs from HECs or duration-adjusted PODs are discussed in sections III.E, IV.E, and IV.F of the Addendum. These UFs account for inter- and intraspecies differences in sensitivities as well as the possibility that infants and children are more sensitive to sulfuryl fluoride than adults.

Lu, comment 6: The use of UFs (10x10) to account for inter- and intra-species differences in the derivation of regulatory standards is well accepted among the regulatory and scientific communities, and has become a gold standard practice in both risk assessment and regulatory settings for the last two decades.

DPR response: No response necessary.

Lu, comment 7: DPR has used HECs aiming to reduce the uncertainty of interspecies pharmacokinetics, which is a one-big step forward to refine the use of UFs in this scenario. However, Reviewer thought the application of HEC in the RfC derivation is not adequate and,

unfortunately, may bring additional uncertainty to the overall derivation. One missing term in converting animal NOEL to POD_{adj} is the lack of taking into account the differences of breathing rate between animals and humans. Since the concern of SF exposure is *via* inhalation for the bystanders in this Addendum, the amount of SF inhaled by the interested individuals shall be incorporated into the conversion of animal NOEL to POD_{adj} . This aspect is identical to the consideration of modifying exposure time in animal studies in accordance with the length of exposure by the bystanders. By taking into account the differences in breathing rate between animals and human in the calculation, the final POD_{HEC} will be closer to reflect the true human equivalent concentrations.

DPR response: DPR has used different approaches to derive RfCs based on the underlying assumption (e.g., systemic or portal of entry effect). Methodologies that account for differences in breathing rate between animals and humans have been presented in our RfC calculations (see Table 1 in the final Addendum). All approaches except for the “No Dosimetric Adjustment” (re-named as unknown mode of action in the final Addendum) have accounted breathing rate differences between animals and humans. For the “No Dosimetric Adjustment,” the between-species differences were instead accounted for by applying a default uncertainty factor (UF) of 10.

Lu, comment 8: DPR has added another UF to address the gap of the database that addresses the pre- and post- natal sensitivity to SF. Such approach has also been employed regularly when regulatory standards were established specifically for protecting sensitive or vulnerable sub-populations, such as childbearing women, infants, and toddlers. However, Reviewer thought the UF of 3x that DPR used in the RfC derivation is too liberal to protect neurological developments from SF exposure during the prenatal and postnatal periods. DPR did address the rationale for adding this UF to the derivation process, however, the use of factor 3x seemed quite arbitrary to the Reviewer. The guess is this factor of 3x was to adjust for the pharmacodynamics difference in which DPR has done so for adjusting the pharmacokinetics difference. Regardless, the Reviewer believes that a factor of 3x for this purpose is less than adequate to protect pre- and post-natal development of brain from SF exposure. Considering brain has been identified as the most sensitive target tissue for SF, the incidence and severity of brain damage depended upon the degree of SF exposure, and the damage in brain during the childhood is likely irreversible, DPR should consider raising this UF to 10x, or higher because of the target tissue that is affected by SF. The UF of 10x has been implemented in the US EPA’s risk assessment for organophosphate pesticides to protect vulnerable sub-populations.

DPR response: DPR chose to reduce the database uncertainty factor (UF_{DB}) from 10 to 3 based on data from the newer non-guideline DNT study and toxicokinetic studies. In the special non-guideline DNT study, F₁ fetuses and pups were not exposed directly to sulfuryl fluoride through inhalation, which is admittedly difficult. DPR has previously acknowledged the complications involved in conducting any inhalation exposure study on such young animals (DPR, 2017a). Even so, results indicated that exposure during gestation and lactation did not necessarily increase the sensitivity to brain lesion formation (see

Appendix C of the final Addendum). Likewise, the toxicokinetic data indicated that exposure during gestation and development did not necessarily yield higher net free fluoride in the brain of younger animals compared to adults. The elevated motor activity found in rat pups at 20 ppm is likely due to pharmacodynamic differences between young and adult rats. The reason for such differences remains unknown, representing a database gap that should be accounted for. Therefore the 3x pharmacodynamic component was retained, resulting in a final UF_{DB} of 3x. A detailed explanation of the UF_{DB} is presented in Appendix C. DPR also elaborates on the UF_{DB} in Section V.E of the final Addendum. While US EPA has retained the full 10x UF for many organophosphate pesticides as Dr. Lu indicated, it is unclear how the agency will account for the results of the special DNT study in estimating the total UF in its upcoming risk assessment for sulfuranyl fluoride.

Lu, comment 9: It is also suggested by the Reviewer that the UF for the gap of database shall be re-named as UF for vulnerability (UF_v), which is the purpose of implementing this UF.

DPR response: It is DPR's convention to refer to the UF for a database gap as UF_{DB}.

Additional minor comments:

Lu, comment 10: This Addendum does not clearly and explicitly define Reference Concentrations (RfCs) for which duration of exposure to sulfuranyl fluoride (SF), acute, short term, sub-chronic, or chronic. The only place the DPR has specifically mentioned about acute reference concentration is in the first paragraph in the Conclusion (page 54). However, based on the calculations shown on page 33, it seemed to Reviewer that DPR's aim was to address the chronic inhalation exposure to humans that are likely to be without appreciable risk of deleterious effects. Reviewer therefore suggested changing RfC to chronic Reference Concentrations, or cRfC so it would not get confuse with RfCs for shorter durations of exposure to SF.

DPR response: DPR has provided a general definition of RfC at the very beginning of the final Addendum (Footnote 1 on pg. 1).

Lu, comment 11: Why brain-to-plasma ration [*sic*] is abbreviated T/P, not B/P ratio?

DPR response: DPR abbreviated brain-to-plasma ratio as T/P (tissue-to-plasma) instead of B/P (brain-to-plasma) because T/P is conventionally used in the literature to refer to any tissue. This designation thus facilitates inter-tissue comparisons. DPR has indicated this in the final Addendum (pg. 45).

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APPENDIX A.

Request for an External Peer Review of the California Department of Pesticide Regulation's Addendum to the 2006 Risk Characterization Document for Sulfuryl Fluoride (Department of Pesticide Regulation Memorandum dated February 28, 2019)

Attachment 2

Description of Scientific Assumptions, Findings, and Conclusions
to be Addressed by the Peer Reviewers

Attachment 2

Description of Scientific Assumptions, Findings, and Conclusions to be Addressed by the Peer Reviewers

Reviewers are asked to determine whether the scientific work product is “based upon sound scientific knowledge, methods, and practices.”

We request that you make this determination for each of the following issues. An explanatory statement is provided for each issue to focus the review.

For those work products which are not proposed rules, as is the case here, reviewers must evaluate the quality of the product using the same exacting standard as if it was subject to Health and Safety Code 57004, which requires highly-qualified experts to perform impartial peer reviews. This is intended to ensure that all proposed CalEPA rule-makings meet accepted standards of the relevant scientific disciplines and to prevent any influence on the rule-makings stemming from irrelevant findings, unwarranted claims, unacceptable interpretations, and personal views.

The assumptions and conclusions used to calculate updated Reference Concentrations (RfCs) for sulfuryl fluoride are discussed in Sulfuryl Fluoride: Draft Addendum to the 2006 Risk Characterization Document-Update of the Toxicology and Reference Concentrations (Addendum). These include the rationale for selection of the critical Points of Departure (PODs), the consideration of plausible routes of entry for sulfuryl fluoride, the approaches for derivation of Human Equivalent Concentrations (HECs) and the choice of appropriate Uncertainty Factors (UFs). Reviewers are requested to review the entire document and make determinations on the scientific methods used to determine each of the following assumptions and conclusions:

- 1. The scientific basis for the proposed RfCs depend both on the nature of the observed effects (non-neurotoxic vs. neurotoxic) and on the assumed mode of action (systemic vs. portal of entry). These issues are addressed in sections III.C, III.D, and Appendix E of the Addendum.**

Non-neurotoxic effects of inhaled sulfuryl fluoride include dental fluorosis, kidney lesions, body weight changes, and thyroid hyperplasia. The mode of action for such effects is likely to be systemic, *i.e.*, mediated by absorption through the respiratory system into the blood followed by transport to target tissues. Additional non-neurotoxic effects include lesions in the respiratory tract (nasal, tracheal, and lung) that likely result from action at the portal of entry. Traditional methodologies for calculating HECs for systemic effects (blood:gas partitioning of inhaled sulfuryl fluoride) and portal of entry effects (regional gas dose ratio for the respiratory tract) are applicable to these cases for derivation of RfCs.

Neurotoxic effects of inhaled sulfuryl fluoride include vacuolation in the basal ganglia, altered

motor activity, tremors and electrophysiological effects. In the past, both DPR and US EPA estimated human health risks for sulfuranyl fluoride based on neurotoxicity. Those assessments assumed that the neurological effects were systemic, with the active principle, fluoride, entering the brain via the blood stream after absorption through the respiratory tract. Dosimetric adjustments for systemic effects were based on the differences in body weight and inhalation rates between animals and humans. Recently, a physiologically based pharmacokinetic (PBPK) model was developed for sulfuranyl fluoride in order to predict brain fluoride concentrations in animals and humans. This model also assumed a systemic route to the target tissue from the respiratory system into the blood. However, the analysis of new data suggested that the neurological effects may be mediated through a direct intranasal-to-brain route that bypasses the blood-brain barrier. This route may not be readily classifiable as systemic (blood-to-brain) or conventional portal of entry (the nasal cavity) effects. Rather, it suggests a portal of entry *subcategory* that involves absorption through the nasal cavity followed by direct access to the basal ganglia (see Conclusion 2).

2. Neurotoxicity of sulfuranyl fluoride can result from direct intranasal transport to the brain rather than through the respiratory system to the blood and then to the brain as discussed in Appendix E of the Addendum.

A direct intranasal route of absorption was supported by the following observations:

- a. Brain-to-plasma (T/P) ratios for fluoride following acute inhalation exposure to sulfuranyl fluoride were approximately 20-fold higher than those following oral, intravenous, or intraperitoneal exposure to fluoride or sodium fluoride.
- b. Brain lesions were confined to the basal ganglia after inhalation exposure to sulfuranyl fluoride, but not after oral exposure to sodium fluoride.
- c. Other inhaled or intranasally administered chemicals are known to access the brain (basal ganglia in particular) via a direct olfactory route.

Two possible pathways could permit direct access of sulfuranyl fluoride (or its ultimate toxicant) to the central nervous system from the point of contact at the nasal epithelium. One is via the olfactory nerve through the rostral migratory stream to the subventricular zone (Appendix E). The other is via extracellular transport, either directly to the basal ganglia or through the cerebrospinal fluid. The possibility that a direct intranasal-to-brain route of absorption for sulfuranyl fluoride is operative prompts the question of which methodology is most appropriate to calculate HECs and RfCs.

3. To account for pharmacokinetic differences between laboratory animals and humans, dosimetric adjustments of air concentrations are necessary precursors to the calculation of RfCs. These are addressed in section III.D of the Addendum.

Due to the uncertainties regarding how sulfuryl fluoride or its hydrolytic products gain access to the brain, different assumptions were necessary to enable dosimetric conversions.

- a. Systemic (blood-to-brain) mode of action: when the neurotoxic effects were assumed to occur through a systemic mode of action, HECs were calculated using either a sulfuryl fluoride PBPK model developed by Dow AgroSciences or a default rat-to-human adjustment factor that assumed blood:gas partitioning of inhaled sulfuryl fluoride to be equal in rats and humans (*i.e.*, $H_{b/g-rat} / H_{b/g-human} = 1$).
 - b. Portal of entry mode of action (acting at the site of contact): when the neurotoxic effects were assumed to occur through a portal of entry mode of action via the nasal cavity, human equivalent concentrations were calculated using a default regional gas dose ratio (RGDR) for the extrathoracic region of 0.064 (US EPA 1994) or 1 (US EPA 2012).
 - c. Direct intranasal-to-brain mode of action: while a direct intranasal-to-brain route is plausible, sufficient data were not available to unequivocally support this mode of action. RfCs were therefore derived directly from duration-adjusted rat PODs, *i.e.*, without first making the dosimetric adjustments necessary for HEC calculations. This was done solely by applying a default uncertainty factor of 10 to the POD to account for interspecies differences.
- 4. UFs used to calculate RfCs from HECs or duration-adjusted PODs are discussed in sections III.E, IV.E, and IV.F of the Addendum. These UFs account for inter- and intraspecies differences in sensitivities as well as the possibility that infants and children are more sensitive to sulfuryl fluoride than adults.**

RfCs were calculated by applying UFs to the critical HEC or POD values appropriate to the assumed mode of action for sulfuryl fluoride (see item 3 for details). The total UF (UF_{total}) was the product of all of the individual UFs. The individual UFs used to calculate the critical RfCs were as follows:

- a. UF_A , animal-to-human extrapolation: This factor assumed that humans are more sensitive than laboratory animals. It defaults to 10 (3 for pharmacokinetic differences, 3 for pharmacodynamic differences) except in cases where dosimetric adjustments were made to account for pharmacokinetic differences, in which case a total UF_A of 3 was applied.
- b. UF_H , intrahuman sensitivity: This factor assumed that there is a 10-fold difference in sensitivity over the entire adult human population. As with the UF_A , the default UF_H of 10 (3 for pharmacokinetic differences, 3 for pharmacodynamic differences) was applied to every assumed MOA.
- c. UF_{DB} , database deficiency: This factor assumed that immature individuals (fetuses, infants and children) were 3x more sensitive than adults to the neurotoxic effects of sulfuryl fluoride. The UF_{DB} of 3 was applied when the critical neurotoxicity study was not conducted using young animals.