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SUBJECT: Response to comments by Dr. Jacqueline MacDonald Gibson 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. Jacqueline MacDonald Gibson of the Department of Environmental Sciences and Engineering in the Gillings School of Global Public Health at the University of North Carolina, Chapel Hill 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. Gibson spent in thoroughly reviewing and commenting on the draft Addendum and two main conclusions (#3, #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

<u>Conclusion 3</u> – ***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.***

Dr. J. Gibson, comment 1: This conclusion is not supported by the available evidence on sulfuryl fluoride toxicity. While in an ideal world it is certainly desirable to adjust air

concentrations to reflect differences in human and animal uptake of contaminants, the available data for sulfuryl fluoride is far too uncertain to support the selection of an appropriate dose adjustment factor. This uncertainty is clearly reflected in Summary Table 1 and Table 14 of the report. This table presents multiple approaches for developing dose adjustment factors. The selected factors range from 0.016 to 1.1 (expressed as the ratio of the no-effect level in animals to the human equivalent concentration). Evidence is insufficient to allow choice of one of these factors over another.

In light of these uncertainties, CalEPA could adopt one of two approaches. The first would be not to adjust the dose, as in the column titled "No Dosimetric Adjustment" in Summary Table 1 and Table 14. A second, more sophisticated approach would be to reflect uncertainty in the dose-adjustment factor using a combination of expert elicitation and Monte Carlo simulation. This alternative approach is illustrated in **Figure 1**.

In the first step of a Monte Carlo simulation approach to characterizing uncertainty in dose adjustment, expert elicitation could be used to assess weights (or probabilities) for each of the possible dose adjustment methods in Summary Table 1. In **Figure 1**, the top left bar chart represents a hypothetical outcome of an expert elicitation experiment. Each bar represents the probability that the dose adjustment method reflects the true state of differences between the test animal and humans. Error bars reflect differences in expert opinion. Prior research has used expert elicitation approaches to account for uncertainty in high- to low-dose extrapolation. For example, Boobis et al. demonstrated how expert elicitation could be used to account for uncertainty in high- to low-dose extrapolation for genotoxic carcinogens (1). A variety of tools has been developed to support expert elicitation that could be used to support this step; a review article by Goossens et al. describes some of these tools and case study applications, including chemical toxicity assessment (2).

In the second step of this Monte Carlo process, probability distributions for each dose adjustment factor in Summary Table 1 could be developed using available experimental data. For example, uncertainty in PBPK model dose adjustments could be estimated using distributions on input parameters for the PBPK model. Mörk and Johanson demonstrate how such probability distributions could be derived if using a PBPK model for converting animal to human doses (3). The four probability distribution functions illustrated at the top right in **Figure 1** represent distributions for alternative approaches to dose adjustment.

In the third step, Monte Carlo simulation could be used to assess combined uncertainty in distributions over possible dose-adjustment methods and, within any given method, parameter uncertainty. The output of this step would be a probability distribution representing the range of values of dose adjustment factors. This output could, if desired, be coupled with additional simulation to represent uncertainty in pharmacodynamics between and within species, as illustrated at the bottom right of **Figure 1** and described further below.

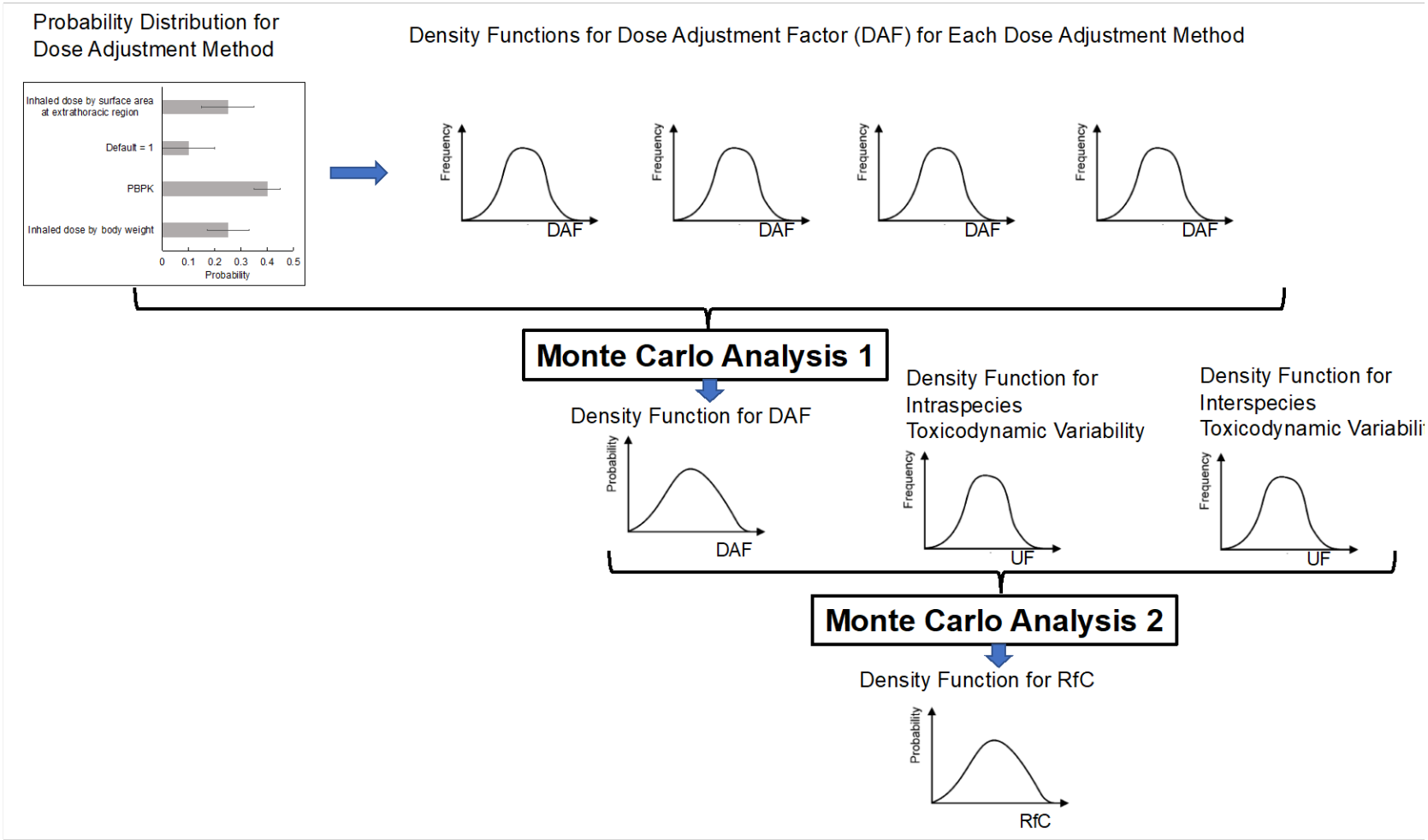

Figure 1. Proposed approach for using Monte Carlo simulation to reflect uncertainty in dosimetric adjustments and intra- and interspecies toxicodynamic variability.

DPR response: DPR acknowledges Dr. Gibson's concern with respect to the uncertainties associated with DPR's various approaches to the derivation of reference concentrations (RfCs). Dr. Gibson suggested two approaches to address these uncertainties: 1) Using "No Dosimetric Adjustment" as DPR proposed in the 2018 Addendum (Summary Table 1); or, 2) Using a combination of expert elicitation and Monte Carlo simulation to reflect uncertainty in the dose-adjustment factor (as illustrated in Figure 1 below).

DPR agrees with Dr. Gibson in that there is insufficient evidence to favor deriving an RfC using one approach over another. Instead, DPR elected to derive RfCs based on the following three assumptions of the mode of action: 1) systemic, 2) portal of entry at nasal cavity (extrathoracic region), and 3) unknown mode of action. This analysis has resulted in a proposed range of acute inhalation RfCs of 0.25 – 0.75 ppm (see Executive Summary Table 1in the final Addendum).

DPR also considers Dr. Gibson's second recommendation to be novel and worthy of future exploration. With respect to sulfuryl fluoride, the use of expert elicitation to assign weights to each possible dose adjustment method is not currently possible, as there are insufficient data to construct density distributions for each mode of action assumption. The main uncertainties accompanying the RfC derivation reside with the mode of action assumptions, the latter which can only be resolved by further experimentation.

<u>Conclusion 4</u> – ***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.***

Gibson, comment 2: The conclusion that uncertainty factors (UFs) are needed to reflect interspecies differences and intraspecies variability is certainly correct. In fact, available scientific evidence suggests that the commonly used default factors of either 3 or 10 (depending on the level of knowledge of such differences) are not always sufficiently protective. For example, in a study of antineoplastic agents, Price et al. found that actual interspecies dose-adjustment factors ranged from 1 to 28 for converting from rat to human doses and from 1 to 63 for converting from mouse to human doses, with 90^{th} percentile values of 16 and 25, respectively (4). In a review of intraspecies differences, Dorne concluded that the current default uncertainty factor for toxicokinetic differences "would not cover human variability for genetic polymorphism and age differences (neonates, children, the elderly)" (5). Based on such evidence, CalEPA is justified in maintaining UFs of at least 10 each for interspecies and intraspecies uncertainty.

Uncertainty in UFs also could be handled via Monte Carlo simulation, in tandem with simulation of pharmacokinetic differences discussed above. Indeed, Kalberlah et al. propose an approach for representing uncertainty in UFs via Monte Carlo simulation (6). **Figure 1**

illustrates how such uncertainty in UFs could be combined with uncertainty in dose adjustments to reflect pharmacodynamic as well as pharmacokinetic differences between and within species.

> **DPR response:** DPR agrees that the default uncertainty factor (UF) of 10 for intraspecies variability is justified for sulfuryl fluoride. We also retained the UF of 10 for interspecies sensitivity when RfCs were calculated without dosimetric adjustment. DPR is aware that probabilistic techniques such as Monte Carlo simulation may provide alternative means for addressing inter- and intraspecies uncertainties, and is considering their use in future risk assessment projects.

Gibson comment 3: It is unclear why CalEPA chose to modify the UF_{DB} (reflecting uncertainty in available data) from the value of 10 used in the RfC for residential bystanders calculated in 2006 to 3 for the newly calculated RfC. It is not clear that studies conducted since 2006 merit this change. On p. 53, the report states, "DPR maintains a practice of applying an additional database uncertainty factor to account for the possibility of increased pre- and post-natal sensitivity when data on young animals are not available." Such data were not available for the study used to establish 300 ppm as the point of departure for estimating an RfC for residential bystanders potentially exposed to sulfuryl fluoride. Indeed, p. 53 of the report notes that in one study, elevated motor activity was detected at a dose of 20 ppm in rat pups, "even while motor activity evaluations in adults under similar exposures were lacking." Given this finding, the change in UF_{DB} from 10 to 3 seems unwarranted.

> **DPR response:** DPR chose to reduce the database uncertainty factor (UF_{DB}) from 10 to 3 is because the newly submitted non-guideline DNT study and toxicokinetic data showed that exposure during gestation and developmental periods did not yield higher brain net free fluoride than exposure in adulthood. Thus, in pharmacokinetic terms, pups are not more sensitive than adults, allowing the pharmacokinetic term of the UF_{DB} to be reduced from 3 to 1. The elevated motor activity found in rat pups at 20 ppm is likely due to a pharmacodynamic difference between young and adult rats. A detailed explanation of this uncertainty factor is presented in Appendix C and in Section V.E. in the final Addendum.

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 sulfuryl 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 sulfuryl 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 sulfuryl 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 sulfuryl 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 sulfuryl 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 sulfuryl 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 sulfuryl 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.