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DATE: May 25, 2020

SUBJECT: Response to comments by Dr. Babasaheb Sonawane 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. Babasaheb Sonawane from the Environmental Metrology and Policy Program at Georgetown University 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. Sonawane spent in reviewing and commenting on the draft and all four main conclusions. 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. B. Sonawane, comment 1: An independent review of literature as it relates to the topics of review was conducted, specifically with a focus on the proposed mode(s) of action of sulfuryl fluoride or fluoride exposure and non-neurotoxic [*sic*] neurotoxic effects. I did not find any new publications directly relevant other than those that are already identified in the

DPR Addendum.

DPR response: No response necessary.

Sonawane, comment 2: The DPR draft Addendum correctly cited, described and applied sound scientific knowledge. It appropriately described currently available and acceptable methods and practices used by the regulatory agencies (USEPA, PMRA) and other international organizations for derivation of RfCs.

DPR response: No response necessary.

Sonawane, comment 3: The unpublished studies in the Attachment 3: Bibliography were independently reviewed and found to be adequately described, and properly evaluated but the conclusions were not well summarized by DPR.

DPR response: The purpose of these newly submitted unpublished studies by the registrant was to develop the physiological-based pharmacokinetic (PBPK) model. DPR has summarized the overall findings from all these studies in the first paragraph of Section II.E.

Conclusion 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.***

Sonawane, comment 4: The references cited in the Addendum, appropriately summarize and are relevant in support of the assumptions made on mode(s) of action for non- neurotoxic and neurotoxic potential effects in humans upon exposure to sulfuryl fluoride. However, the Addendum does not provide enough information on the approach/process and/or methods used to conduct a systematic review of literature. Specifically, in Appendix E, Point 4: Existence of a direct intranasal route to brain tissue in the literature. This section is not systematically presented, making it difficult to follow how the references cited were selected and what criteria were used for their inclusion/exclusion. A brief overview, including evidence with references and a presentation of MOA studies relevant to the inhalation exposure of biological active molecules, followed by fluoride and sulfuryl fluoride in experimental animals and humans could improve the discussion of this section.

DPR response: For purposes of this Addendum, we did not conduct a systematic review of the literature on the intranasal pathway, focusing instead on the data supporting the possible modes of action for toxicity following sulfuryl fluoride inhalation. A systematic review would likely provide a more comprehensive understanding for a direct nasal-to-brain route. However, this route has been thoroughly covered in the literature for other compounds and xenobiotics, including in a recent review by Crowe *et al.* (2018). It is our professional opinion that the peer-reviewed studies on the intranasal pathway cited in the Addendum showed no significant flaws in methodology, data collection or analysis, nor with the conclusions. Following the external review, we have restructured Appendix E to focus on the

possible entry routes of sulfuryl fluoride and/or its metabolites from the nasal cavity to the brain. We have also indicated that confirmative data for any particular pathway are currently lacking (see Appendix E in the final Addendum).

Sonawane, comment 5: Recommend to replacing the word "Existence" to "Plausible Evidence" in the title of Appendix E, Point 4. Also consider adding the following text in the introductory paragraph: "The olfactory system receptors are more or less directly exposed to the outside environment, some xenobiotics can enter the brain via the olfactory nerve or surrounding perineural spaces, bypassing the blood-brain barrier and damaging the CNS structures and resulting in pathological changes." The DPR review of new literature on the topic of mode of action makes an argument for a direct intranasal to brain transport of sulfuryl fluoride/ fluoride, however, it remains speculative at best. There is no direct demonstrated experimental evidence for neurological effects of either for sulfuryl fluoride or fluoride exposure that may be mediated through a direct intranasal- to -brain route bypassing the blood-brain barrier for neurological effects. Therefore, I suggest a wording change of the conclusion in Attachment 2, point #2, page 5 from "can" to "may likely." Given several limitations and uncertainties and a lack of direct evidence for intranasal to brain tissue as correctly pointed out in the Addendum, I believe, the DPR argument is weaker for using this MOA for derivation of RfCs regardless of good evidence described for several other xenobiotics.

DPR response: DPR has incorporated Dr. Sonawane's editorial comments in Appendix E. DPR also agrees with Dr. Sonawane that there is no current evidence for neurological effects mediated through a direct nasal-to-brain route for sulfuryl fluoride. This point is noted throughout the Addendum. In addition, the postulated intranasal mode of action (MOA) was not used to derive an acute reference concentration (RfC). In the final Addendum, DPR underscored the uncertainty of a direct intranasal MOA when discussing different approaches to dosimetric calculating a human equivalent concentrations and RfCs.

Sonawane, comment 6: Appendix E. Point 4: Existence of a direct intranasal route to brain tissue in the literature: The DPR authors of the Addendum have clearly identified and discussed uncertainties and limitations for intra-nasal to brain route of delivery of fluoride or sulfuryl fluoride gas. Research needs and suggestions for additional studies are very well articulated.

DPR response: No response necessary.

Conclusion 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.***

Sonawane, comment 7: The DPR Addendum did an excellent job describing and correctly accounting for the pharmacokinetic differences between laboratory animals and humans and made appropriate dosimetric adjustments for air concentrations to the calculation of RfCs. The default uncertainty factors selected for short-term and acute exposure studies and to account

for animal to human extrapolation, intra-human sensitivity, and database deficiency are very well described and justified, and have been appropriately applied for derivation of RfCs.

DPR response: No response necessary.

Sonawane, comment 8: In my opinion, the underlying assumptions of the PBPK model may be invalid thus, the model could not be used to support reducing the uncertainty factor. The PK studies and results are well described, however, there is need to summarize the conclusions along with major uncertainties for the Section D. Pharmacokinetics.

DPR response: DPR agrees with Dr. Sonawane with respect to the uncertainties underlying the PBPK model. These are addressed in Appendix F. Conclusions from the pharmacokinetic (PK) studies are summarized in Section II.E.

Sonawane, comment 9: The PBPK model is not fully validated with independent data and the assumed values of fractional inhalation absorption in rabbits and humans are uncertain, therefore, the prediction alone may be insufficient to address the concern with respect to the developmental neurotoxicity.

DPR response: DPR agrees with Dr. Sonawane's comments. These uncertainties are addressed in Appendix F.

<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.***

Sonawane, comment 10: The estimated inhalation reference calculations for the non-neurotoxic and neurotoxic effects for different durations of exposure were independently checked. All of them were found to be well documented and correct.

DPR response: No response necessary.

Sonawane, comment 11: There is uncertainty regarding the lack of an acute neurotoxicity study in immature animals: Calculation of acute RfCs utilized an additional database uncertainty because the critical neurotoxicity study was not conducted using young animals, leaving the possibility that enhanced sensitivity in young animals was not accounted for. An assessment of cognitive function in developing young after exposure to sulfuryl fluoride was not performed. Therefore, overall residual uncertainty remains concerning the susceptibility of young children and other highly susceptible individuals in the population to potential neurotoxic effects later in life following acute, episodic and/or repeated early-life exposure to sulfuryl fluoride even the database uncertainty factor may account for this concern.

DPR response: DPR acknowledged the uncertainty regarding the possibility of enhanced sensitivity in young animals in Section V.E. of the final Addendum. Briefly, a database uncertainty factor (UF_{DB}) of 3 accounts for the possibility of increased pharmacodynamic sensitivity in immature animals. We considered the pharmacokinetic aspect of the UF_{DB} to be 1 based on similar brain fluoride concentration between young and adult rats (Appendix C).

Additional comments and suggestions:

Sonawane, comment 12: DPR needs to clearly state the definition of RfC used by the CalEPA, if it is different from the US EPA. For example, The US EPA defines RfC as estimates with uncertainty (spanning perhaps an order of magnitude) of continuous inhalation exposures to the human population (including sensitive subgroups) that are likely to be without appreciable risk of deleterious effects during lifetime. These values are calculated by dividing the critical endpoint concentrations (points of departure, POD) by the uncertainty factors appropriate to the exposure scenarios evaluated. The commonly used default uncertainty factors are 10 for interspecies sensitivity and 10 for intraspecies variability. Additional uncertainty factors may be applied to account for sub-chronic to chronic exposure, LOAEL to NOAEL and data gaps.

DPR response: DPR has clearly defined the definition of RfCs in Footnote 1 of the final Addendum (pg. 1), as noted here:

"Reference concentrations (RfCs) are target air concentrations. They are estimates of inhalation exposures to humans that are likely to be without appreciable risk of deleterious effects. These values are calculated by dividing the critical endpoint concentrations (points of departure, POD) by the uncertainty factors appropriate to the exposure scenarios evaluated. The commonly used default uncertainty factors are 10 for interspecies sensitivity and 10 for intraspecies variability, which can be adjusted based on available data of pharmacokinetics or pharmacodynamics. Additional uncertainty factors may be applied to account for data gaps."

Sonawane, comment 13: Suggest changing Table 1 title to Summary of Acute reference concentrations (RfCs) for residential bystanders (DPR and US EPA)

DPR response: The original summary Table 1 has changed its content, and the title for the new Summary Table 1 is "Proposed regulatory targets for sulfuryl fluoride for residential bystanders (acute reference concentrations, RfCs)."

Sonawane, comment 14: Recommend revising the Oncogenicity section to the following: "The conclusion that sulfuryl fluoride is not carcinogenic remains the same as that expressed in DPR's 2006 RCD. However, fluoride is considered a principal toxicant and there are number of studies in the published literature on potential carcinogenicity of fluoride in humans and laboratory animals (see review by NRC, 2006). Nonetheless, there may be some epidemiological evidence that fluoride may be associated with osteosarcoma

in young males (Cohn, 1992; Maurer et al, 1993; Bassin et al, 2006), but several confounding factors limit the interpretation of these studies. An updated review by the National Research Council (NRC, 2006) failed to reach an unequivocal conclusion on this issue in light of mixed findings from animal and human studies, genotoxicity assays, and mechanistic studies. The 2006 NRC report concluded that "The combined literature does not clearly indicate that fluoride either is or not carcinogenic in humans". The Cohn (1992) ecological study findings were published as a report, (not peer-reviewed) based on analysis of a limited number of cases of osteosarcoma in males under age 20, and no increased risk was observed in females, exposure was only based on residence at the time of cancer diagnosis and no details of statistical analysis was provided. An epidemiological study found a positive association between estimated fluoride exposure in the drinking water and incidence of osteosarcoma in 6 to 8-year-old boys (Bassin *et al.*, 2006). This study examined data from a hospital-based case-control study collected between 1989 to 1992. However, a separate study that examined another set of osteosarcoma cases collected between 1993 and 2000 at the same hospitals did not demonstrate a significant association between bone fluoride levels and osteosarcoma risk (Kim *et al.*, 2011). The major advantage of the latter study is the use of bone fluoride concentrations as the measure of fluoride exposure, rather than estimating fluoride exposure in drinking water (ATSDR, 2003; Bassin *et al.*, 2006). However, bone fluoride levels were only measured at a single time point (total accumulated dose). As such, it is difficult to evaluate the exposure-effect relationship and what the critical window of time for fluoride exposures may be. In addition, epidemiological studies of inhalation exposure to hydrogen fluoride and fluoride dust also concluded that carcinogenicity via inhalation of fluoride is unlikely (ATSDR, 2003). There are nine rodent bioassay studies for carcinogenicity of fluoride, and they have been well summarized in the Chapter 10, pp. 316-320, Attachment 2 of the NRC (2006) report. It is widely recognized that the fluoride exposure and osteosarcoma connection is biologically possible since fluoride is known to stimulate osteoblasts (bone forming cells) and may increase the risk of bone cancer."

DPR response: DPR has incorporated several of these suggestions into Section II.D. of the final Addendum which discusses the potential for oncogenicity (see pg. 21-22).

"The conclusion that sulfuryl fluoride is not carcinogenic remains the same as that expressed in DPR's 2006 RCD. Because fluoride is considered as the principal toxicant of sulfuryl fluoride, DPR reviewed literature updates on fluoride carcinogenicity. It is acknowledged that the fluoride exposure and osteosarcoma connection is biologically possible since fluoride is known to stimulate osteoblasts (bone forming cells) and may increase the risk of bone cancer. There are epidemiological evidence showing that fluoride may be associated with osteosarcoma in young males, but several confounding factors limit the interpretation of these studies (Bassin *et al.*, 2006; Cohn, 1992; Maurer *et al.*, 1993). An updated review by the National Research Council (NRC, 2006) failed to reach an unequivocal conclusion on this issue in light of mixed findings from animal and human studies, genotoxicity assays, and

mechanistic studies. The 2006 NRC report concluded 'The combined literature does not clearly indicate that fluoride either is or not carcinogenic in humans (pg. 284).'"

Sonawane, comment 15: Suggest changing the Title of Table 10 to Summary of Short-Term (10-14 days) inhalation.

DPR response: Revised as suggested (Table 12 in the final Addendum).

Sonawane, comment 16: For the sake of clarity, in each section of II. Toxicological Profile, I recommend including a brief statement of the conclusion(s) from the 2006 RCD. In addition, provide a clear statement that confirms earlier findings either concurring with the 2006 RCD or provide a conclusion, if it is different from it.

DPR response: DPR has indicated in Section II. Toxicological Profile that only new data and/or new analyses are discussed in the Addendum. Studies evaluated in the 2006 RCD are not re-reviewed in the Addendum. With respect to genotoxicity and oncogenicity, DPR has included a brief statement of conclusion from the 2006 RCD and noted the concordance or discordance between the Addendum and the 2006 RCD where necessary. With respect to pharmacokinetics, only one rat study was available for review in the 2006 RCD. To provide clarity, DPR has incorporated its main findings in the beginning of Section II. No developmental neurotoxicity studies were reviewed in the 2006 RCD. However, per the reviewer's request, DPR has provided a general conclusion based on the integration of all related studies reviewed in the 2006 RCD and the final Addendum, as noted here (see pg. 21):

"Based on findings from this study, pharmacokinetic studies reviewed in this Addendum, and the developmental and reproductive toxicity studies reviewed in the 2006 RCD, DPR concludes that there is no evidence for increased pharmacokinetic susceptibility to the young, but uncertainties in pharmacodynamics remain (see Appendix C)."

Sonawane, comment 17: Accidental exposure or intentional release of sulfuryl fluoride may pose a serious hazard to the respiratory and CNS systems, however, dermal uptake as a secondary route is a public health concern and needs to be recognized in the Addendum. A literature search is suggested, and evaluation of relevant studies needs to be included. There is some limited evidence for skin absorption. For example: Gaskin et al; 2017. Toxicol. Ind. Health. 33(7): 547- 554) publication is suggested for review and inclusion in the Addendum.

DPR response: DPR is not aware of effects resulting from dermal exposure to sulfuryl fluoride. A registrant submitted acute study in rats showed no toxicity following dermal exposure to the highest vapor concentration tested (9599 ppm) (Bradley *et al.*, 1990). Gaskin *et al.* (2017) concluded that there was no evidence for skin penetration of sulfuryl fluoride for up to 30 min of exposure at the highest concentration of 5000 ppm. Because the purpose of this Addendum is to update the acute inhalation RfC for residential bystanders exposed through structural fumigation, other exposure scenarios are not addressed. Please also note

that expanded background information on mitigation of inhalation exposures following structural fumigation have been added to the final Addendum (see pg. 5 – 7).

Sonawane, comment 18: Recommend adding the following statement at the end of II. A. Developmental Toxicity section: "In conclusion, the results of the developmental and reproductive toxicity studies conducted so far did not provide evidence for increased susceptibility to the young."

DPR response: DPR reviewed the sulfuryl fluoride database for susceptibility to immature individuals in Appendix C. From this, DPR concludes there is no evidence for increased susceptibility to young animals that could be explained through pharmacokinetic analysis. In other words, there was no demonstrable difference in brain fluoride concentration between young and adult rats (see response to comment 16 above). However, uncertainties stemming from possible pharmacodynamic differences could not be excluded (see Section V.E.2).

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.