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SUBJECT: Response to comments by Ensystex II, Inc. on DPR's draft Addendum to the 2006 Sulfuryl Fluoride Risk Characterization Document dated December 2018

I. Background

On March 21, 2019, Ensystex II, Inc. submitted comments to the Human Health Assessment (HHA) Branch of the California Department of Pesticide Regulation (DPR) on the December 2018 draft Addendum to the 2006 Sulfuryl Fluoride Risk Characterization Document. DPR appreciates the efforts taken by Ensystex to review the draft Addendum. This memorandum summarizes the comment received along with DPR's response. The final Addendum referenced refers to DPR's final June 2020 Addendum to the Sulfuryl Fluoride Risk Characterization Document.

II. Response to Comments

Ensystex II, Inc. comment: My number one concern in this document is on page 34 where you introduce "3) unknown route of entry. For the alternative "unknown" approach, no dosimetric adjustments were used to calculate a neurotoxicity HEC. Instead, the RfC derivation for neurotoxic effects is based on a duration adjusted POD from the animal study combined with uncertainty factors for inter- and intraspecies extrapolation (UFA and UFH, 10x each)."

This being something completely new, I believe this needs to be discussed and clarified before implementation of any changes to the use of sulfuryl fluoride in California.

DPR response: We approached the calculation of the sulfuryl fluoride reference concentration (RfC) using several different methodologies to reflect the most recent advances in animal to human equivalency and the currently available data. There are several potential pathways involved in the neurotoxic response to inhaled sulfuryl fluoride. These include the absorption into blood through the respiratory tract followed by delivery of toxic metabolites to brain (systemic mode of action) and direct entry into brain from the nasal cavity (portal of entry mode of action). In addition, it is possible that a local vascular pathway may be involved, by which brain access occurs following nasal absorption and subsequent uptake into local neurovascular networks. Our analysis of available data did not allow us to clarify which of these pathways, either alone or in combination, led to neurotoxicity following inhalation exposure to sulfuryl fluoride. Because fluoride delivery may occur by multiple routes, we included an RfC derivation methodology that did not assume a specific mode of action. This was described in the draft Addendum (December 2018) as the alternate unknown approach, as quoted above.

The calculation of an RfC in the absence of a clear mode of action is not new. DPR has used this approach in the past for inhaled toxicants, generally because of database insufficiency. Such an approach requires only an experimentally-derived (animal) point of departure and relevant uncertainty factors. This approach was used most recently in the 2014 risk assessment for phosphine.

Following receipt of stakeholder comments and completion of the external scientific review, we expanded the description of the uncertainties underlying each RfC approach in the final Addendum. We have proposed three distinct RfCs for possible use as regulatory targets. These values are based on three possible modes of action: 1) systemic, 2) portal of entry from the nasal cavity, and 3) an unknown mode of action. The resulting range of values is 0.25 – 0.75 ppm. This is summarized in Executive Summary Table 1. Supporting scientific information, including description of the toxic metabolites and alternative pathways for delivery of fluoride from the nasal cavity to brain, are detailed in Appendices G and E.