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A Revised Allowable Limit (AL) for Ethylene Oxide (EtO) Exposure in Children for Limited Duration Exposure Medical Devices According to ISO 10993-17:2023 and 10993-7:2008

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Background and Purpose: Ethylene oxide (EtO) is a colorless gas that is used to sterilize medical devices that cannot be sterilized *via* steam or radiation. In humans and/or animals, EtO has been shown to adversely effect neurological, hematological, respiratory, endocrine, and reproductive and developmental endpoints. Currently, the risk assessment framework outlined in ISO 10993-7:2008 and 10993-7:Amd.1:2019 states that the EtO (Chemical Abstracts Service Number [CAS No.] 75-21-8) sterilization residual tolerable intake (TI) is 0.3 mg/kg-bw/day for both limited (≤24 hours) and prolonged (2-30 days) exposure durations. These acute and chronic TIs are both based on non-cancer effects (decreased maternal and fetal body weights) associated with repeated exposure to EtO *via* intravenous (IV) or inhalation routes in rabbits and rats, respectively. Considering a child's lack of sexual maturity to reproduce a developing fetus, these effects may not be the most relevant for establishing a TI for this specific patient population. Furthermore, ISO 10993-7:2008 calculates an acute EtO TI using an intraspecies uncertainty factor (UF) of 30 to account for variable susceptibility between genotypes and other determinants (*i.e.*, defective DNA repair, poor nutritional state). The relevance of factors identified as increasing interindividual variability for the specific case of an acute exposure in a pediatric patient population has not been considered previously. The Final Draft International Standard (FDIS) ISO 10993-7 suggests that the risk assessment framework within ISO 10993-17:2023 may be used to derive an alternative TI for EtO. This case study derives an alternative allowable limit (AL) for limited (≤24 hours) duration exposures to EtO in children (minimum body weight of 10 kg). With the risk assessment framework based on the Agency for Toxic Substances and Disease Registry (ATSDR) association of key hazards with acute *vs.* repeated exposures to EtO, taking into account variable susceptibility within the intended patient population (children), a revised TI and AL specifically for limited (≤24 hours) duration exposures to EtO in children (minimum body weight of 10 kg) is proposed herein.

Methods: To establish a justifiable point of departure (POD) for acute exposures in a pediatric patient population in accordance with ISO 10993-17:2023, a literature review was conducted that leveraged assessments completed by other health authorities for this case study. Literature searches were conducted *via* the data aggregator ToxPlanet (a federated search engine that extracts content from more than 500 websites), as well as general Internet searches, which typically included the following sources: the Hazardous Substances Data Bank (HSDB), ATSDR, GENE-TOX Data Bank hosted by the National Library of Medicine (NLM), Chemical Carcinogenesis Research Information System (CCRIS), United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), International Toxicity Estimates for Risk Assessment (ITER), Organisation for Economic Co-operation and Development (OECD) Screening Information Dataset (SIDS) assessments, European Chemicals Agency (ECHA), European Food Safety Authority (EFSA), High Production Volume Information System (HPVIS), and Registry of Toxic Effects of Chemical Substances (RTECS). Additional searches of PubMed and Google were also performed. The search terms included each chemical's CAS No. and/or name. Following selection of an appropriate health protective POD, the relevance of factors identified as

increasing interindividual variability for the specific case of an acute exposure in a pediatric patient population were considered, namely the role of glutathione S-transferase theta-1 (GSTT1) polymorphisms, the role of epoxide hydrolase (EH) polymorphisms, inhibition of EtO detoxification enzymes, glutathione (GSH) levels, and polymorphisms of DNA repair capacity.

Results: Based on a review of the EtO toxicity literature, the most sensitive hazards associated with acute EtO inhalation exposure were identified as developmental and neurological effects. Considering a child's lack of sexual maturity to reproduce a developing fetus, the most relevant hazard associated with acute exposure is neurotoxicity. A key study was identified where Sprague Dawley rats (n = 10/sex/dose) were administered 1, 100, 300, and 500 ppm of EtO *via* inhalation for 6 hours. The no observed adverse effect concentration (NOAEC) was determined to be 100 ppm (equivalent to 27.6 mg/kg-bw/day), based on decreased alertness and motor activity in both sexes at doses ≥300 ppm. This hazard endpoint and no observed adverse effect level (NOAEL) are considered health protective for pediatric populations under acute exposure duration scenarios. In accordance with ISO 10993-17, UFs were then considered to address both intra- and interspecies variability. Consistent with ISO 10993-7, an interspecies UF of 1 is justified based on data from the physiologically based pharmacokinetic (PBPK) models suggesting the internal doses in mice, rats, and humans are roughly equivalent following inhalation exposure to given concentrations of EtO. ISO 10993-7:2008 then applied a UF of 30 to account for interindividual variability due to possible increased susceptibility associated with GSTT1 polymorphisms, EH polymorphisms, inhibition of EtO detoxification enzymes, GSH levels, and polymorphisms of DNA repair capacity. Regarding variable GSTT1 polymorphisms, published PBPK models demonstrate that inhibition of GSTT1 would have negligible impact on venous blood concentrations of EtO in humans. Regarding variable EH polymorphisms, studies in the published literature suggest that some degree of interindividual variability exists, and that most of the population would be encompassed by a 10-fold range. Furthermore, certain disease states may be associated with a 50% inhibition of EH detoxification activity. However, even considering a 50% reduction in EH capacity, the equivalent capacity to metabolize EtO is roughly 819 µg EtO per mg microsomal protein per day, or 2,407 mg EtO/day for a child (assuming 2,940 mg microsomal protein). This detoxification capacity, even at conservatively reduced levels, is not anticipated to yield clinically relevant impacts at EtO exposure levels near the proposed TI level. Regarding GSH, data similarly suggests a low likelihood of clinically relevant impact on tolerability to EO exposure. For example, even a 40% decrease from normal homeostatic levels (~5-15 mM) would still result in millimolar levels of GSH. Considering GST requires 1 mole of GSH per conjugation reaction with 1 mole of xenobiotic, these reduced GSH levels are not anticipated to result in increased susceptibility to EtO concentrations near the derived TI value. Lastly, while DNA repair polymorphisms may impact potential cancer risks, this endpoint is not relevant for a limited contact ≤24 hour exposure duration device. Taken together, a cumulative UF of 10 is proposed to account for potential interindividual variability associated with acute exposure to EtO in pediatric patients for this case study. This proposed approach yields a TI of 0.552 mg/kg-bw/day, and an AL of 5.52 mg/day for limited (≤24 hours) duration exposure to EtO in children (minimum body weight of 10 kg).

Conclusions: This case study proposes an AL specific for potential acute (<24 hours) exposures to EtO in a pediatric patient population (body weight of 10 kg). This AL is based on a key hazard (neurotoxicity) most relevant for the intended exposure duration and patient population. UFs are then applied accounting for potential inter- and intraspecies variability. The data suggests that even when accounting for GSTT1 polymorphisms, decreases in EH activity, and reduced GSH levels, a revised AL of

5.52 mg/day conservatively evaluates the potential risk to children (body weight of 10 kg) associated with limited (<24 hours) duration exposure to EtO residuals, and supports a conclusion of low toxicological risk associated with this approach methodology.