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Risk Assessment of 1,1,1-Trifluoroethane (HFA-143a) as a Potential Impurity in HFA-134a in Metered Dose Inhaler Products

Asthma prevalence in the United States has been steadily increasing in recent decades. According to a survey conducted by the Centers for Disease Control (CDC) in 2017, about 25 million people in the US, or 8% of the population, suffer from asthma. Treatments delivered by pressurized metered dose inhalers (pMDI) are the cornerstone of symptom management among asthma patients. The compound 1,1,1,2-tetrafluoroethane (HFA-134a) is a commonly used propellant in pMDIs. Here, we derived a permissible daily exposure (PDE) of 1,1,1-trifluoroethane (HFA-143a) as a potential impurity in HFA-134a and compared this to the current US Food and Drug Administration (US FDA) accepted specification for HFA-134a. Standard risk assessment methodology was followed, and the PDE was derived in accordance with available International Conference on Harmonisation (ICH) guidance. We determined that HFA-143a is not expected to be mutagenic or carcinogenic based on *in vivo* and *in vitro* mutagenicity and genotoxicity studies and a two-year chronic oral exposure study, in which the no-observed adverse effect level (NOAEL) was > 300 mg/kg bw/day, the only dose tested. No signs of developmental and reproductive toxicity were reported from inhalation exposure to HFA-143a in studies with rodents and rabbits. The most sensitive endpoint was determined to be cardiac sensitization hazard. In an acute inhalation study with beagle dogs, cardiac sensitization responses were observed with a no-observed adverse effect concentration (NOAEC) of 250,000 ppm, equivalent to a delivered dose NOAEL of 3,716 mg/kg. However, the two-year chronic study would provide a more appropriate point of departure for risk assessment given potential chronic pMDI use. Based on a NOAEL of 300 mg/kg determined from the two-year chronic oral exposure study, a PDE of 0.6 mg/kg was derived. We compared this PDE to the US FDA accepted impurity concentration of 20 ppm for HFA-143a in clinical-grade HFA-134a. Assuming an HFA-143a concentration of 20 ppm is delivered in one 50 µL pMDI actuation, a safety margin of 25,510 is derived. These results strongly suggest that the US FDA accepted concentration of 20 ppm for HFA-143a provides appropriate protection against potential adverse health effects caused by HFA-143a as a potential impurity in an HFA-134a pMDI.