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SUBJECT: Acephate: Acute reference dose (RfD) and reference concentration (RfC) determinations

Introduction

The purpose of this memorandum is to provide the RfD (oral and dermal routes) and RfC (inhalation route) values necessary to develop risk mitigation strategies for occupational exposure to the organophosphate (OP) insecticide acephate. In 2008, DPR issued a comprehensive risk assessment document on this chemical that identified a critical acute oral NOEL (DPR 2008). This value---1 mg/kg/day based on inhibition of plasma and RBC cholinesterase activities in a human oral study (Freestone and McFarlane, 2001)---was used to estimate risks from acute oral exposures as well as from short-term occupational exposures by the dermal and inhalation routes (DPR 2009, DPR 2013). At the time, the target MOE was set at 10 to account for possible intrahuman variations in sensitivity.

However, in 2015 US EPA conducted a systematic review of the literature to determine if developmental neurotoxicity was associated with OP pesticides (US EPA, 2015). Results from toxicity studies in animals, as well as mechanistic and human epidemiology studies, showed that OPs interfere with several biological pathways that are critical for normal brain development. Most of these studies investigated potential neurodevelopmental effects in infants and children following prenatal exposure to the well-characterized OP pesticide chlorpyrifos. This review associated behavioral effects in animals with possible neurodevelopmental outcomes in humans such as attention deficit hyperactivity disorder (ADHD), behavioral problems and autism spectrum disorders. Because of the uncertainty as to whether exposures below those that result in cholinesterase (ChE) inhibition may produce developmental neurotoxicity, US EPA retained the Food Quality Protection Act (FQPA) factor of 10 for many OPs including acephate. Based on

US EPA's systematic review, HHA also recommends an additional developmental uncertainty factor of 10 when evaluating exposure to females of childbearing age. Thus a combined target MOE of 100 (10x intrahuman, 10x developmental) is appropriate for evaluating acephate's risks to occupational populations.

Calculation of the acute oral RfD

Because absorption by the oral route was considered to be 100%, the acute oral RfD is the critical NOEL divided by the combined uncertainty factor:

$$\text{acute RfD}_{\text{oral}} = 1 \text{ mg/kg} \div 100 = \mathbf{0.01 \text{ mg/kg/day}}$$

Calculation of the dermal RfD

Because the human oral study was considered by DPR to be the most appropriate for calculating a dermal RfD, the critical oral NOEL of 1 mg/kg/day is still applicable. However, because dermal absorption is 7.6% (DPR, 2009; DPR, 2013), the dermal RfD (*i.e.*, the *external* dermal dose that would result in an internal dose of 0.01 mg/kg/day) is equal to the oral RfD times 100/7.6:

$$\text{acute RfD}_{\text{dermal}} = 0.01 \text{ mg/kg} \times 100/7.6 = \mathbf{0.13 \text{ mg/kg/day}}$$

Calculation of the inhalation RfC

Because the human oral study was also considered by DPR to be the most appropriate for calculating an inhalation RfC, the critical oral NOEL of 1 mg/kg/day is still applicable since inhalation absorption is assumed to be 100% (DPR 2008, DPR 2013). However, for the inhalation route, an acute internal RfD must be converted to an RfC by taking into account the default adult inhalation rate of 0.28 mg^3/kg/day, which is equal to 0.09 mg^3/kg/8-hr workday (DPR 2013, Andrews and Patterson, 2000):

$$\text{acute RfC}_{\text{inhalation}} = 0.01 \text{ mg/kg} \div 0.09 \text{ m}^3\text{/kg/8-hr day} = \mathbf{0.1 \text{mg/m}^3}$$

Appraisal

The 2008 risk characterization document for acephate evaluated acute dermal and inhalation risk using a critical NOEL from an acute oral study in humans. While use of the human study avoided uncertainties pertaining to species extrapolations, it added uncertainty due to exposure route extrapolations.

It is important to note that the RfD and RfC values calculated in this memorandum apply only to individual exposure routes when each is considered separately. In the event that an occupational

worker may be exposed to acephate by more than one route at a time (e.g., dermal and inhalation, oral and dermal, etc.), the proposed RfCs and RfDs may not necessarily be protective. The internal dose of 0.01 mg/kg/day should not be exceeded in either single exposure scenarios or in aggregate exposure scenarios.

Table 1. Revised acute/short-term NOEL, RfD and RfC values for acephate

Occupational exposure scenarios (routes and duration)	RBC and plasma ChE inhibition in humans		
	NOEL[a] (mg/kg)	RfD (mg/kg/day)	RfC (mg/m^3)
Uncertainty factors (UF)[b]	-	1 inter 10 intra 10 DNT	1 inter 10 intra 10 DNT
Acute/short-term - oral	1	0.01	-
Acute/short-term - dermal[c]	1	0.13[e]	-
Acute/short-term - inhalation[d]	1	-	0.1[e]

a/ Single dose, oral capsule in humans, (Freestone & McFarlane, 2001)
b/ Uncertainty factors include a 10X factor for potential developmental neurotoxicity (DNT) associated with organophosphate pesticides (U.S. EPA, 2015), 1X for interspecies extrapolation (inter) and 10X for intraspecies variability (intra).
c/ Inhalation: Route specific inhalation RfC: oral dose (mg/kg/day) / Breathing Rate (BR) for 8 hour workday; Oral NOEL=1 mg/kg/day; BR=0.09 mg^3/kg/8-hr workday (Andrews and Patterson, 2000)
d/ Dermal: Route specific dermal NOEL is based on dermal absorption in humans of 7.6% (DPR 2009, DPR 2013)
e/ Route to route extrapolation

References

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