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DATE: August 15, 2016

SUBJECT: Update to the Critical Subchronic and Chronic Points of Departure and Associated Reference Exposure Levels Evaluated in the 2003 Methyl Isothiocyanate Risk Characterization Document

I. Introduction

In the finalized Risk Characterization Document (RCD) for methyl isothiocyanate (MITC) dated July 25, 2003, the critical subchronic and chronic no-observed-effect levels (NOELs) were determined using a human daily exposure duration of 24 hours/day for 7 days/week, a default that is now considered appropriate only for bystanders and the general public. Occupational exposure durations are generally assumed to be 8 hours/day for 5 days/week. Based on the use pattern, seasonal workers were assumed to be exposed to MITC for 120 days per year. This memorandum revises the occupational subchronic and chronic NOELs and recalculates the margins of exposure (MOEs) for those populations. In addition, new occupational reference exposure levels (RELs) are generated.

II. Subchronic / chronic NOEL calculations

The RCD describes the NOEL calculation as follows[1]:

> A 6-hour/day, 5-days/week lowest-observed-effect level (LOEL) of 1700 ppb (1.7 ppm) based on nasal epithelial atrophy was identified in the 4-week rat inhalation study of Klimisch *et al.* (1987). To convert this LOEL to the more useful 24 hours/day, 7 days/week value, an extrapolation utilizing Haber's Law was invoked:

[1] Risk Characterization Document (RCD) for Methyl Isothiocyanate (MITC) following the Agricultural Use of Metam Sodium, California Department of Pesticide Regulation, July 25, 2003, p. 74. Available at http://www.cdpr.ca.gov/docs/risk/rcd.htm

1. An equivalent human 6-hour subchronic inhalation LOEL was estimated by multiplying the rat LOEL (1700 ppb) by 5/7 to correct for the 5 days/week exposure regimen. Thus,

$$(1700 \text{ ppb}) \times (5 \text{ days} / 7 \text{ days}) = 1214 \text{ ppb}$$

2. A 24-hour subchronic inhalation LOEL was calculated from the 6-hour value by invoking Haber's Law, with n set to a default value of 1,

$$C^n \times T = K, \text{ Haber's Law}$$

C = concentration, n – chemical-specific adjustment factor set arbitrarily at 1 [an empirical value is not known], T = exposure time, K = constant

$$1214 \text{ ppb} \times 6 \text{ hr} = 7284$$
$$C^1 \times 24 \text{ hr} = 7284$$
$$C = 304 \text{ ppb} = \text{LOEL} [\approx 300 \text{ ppb}]$$

A default uncertainty factor of 10 is usually applied when estimating a NOEL from a LOEL value. However, in the present case, where there is considerable question about the interpretation of the determining endpoint (nasal epithelial atrophy), an uncertainty factor of 3 was considered appropriate. Thus 100 ppb (*i.e.*, 300 ppb ÷ 3) was designated as the critical estimated NOEL for subchronic toxicity. It was used in the evaluation of risks inherent in seasonal exposure to MITC in residents and bystanders. Furthermore, a chronic NOEL of 10 ppb was estimated by dividing the subchronic NOEL (100 ppb) by a default uncertainty factor of 10.

III. Revised calculation of occupational subchronic / chronic NOELs

As noted in the introductory paragraph, those NOELs should only be applied to exposure scenarios involving bystanders and the general public. NOELs for worker scenarios would be calculated similarly, but employ a time factor of 6/8 (*i.e.*, 6 hours/day animal exposure time and 8 hours/day potential worker exposure) rather than 6/24. Additionally, the 5/7 factor used in the bystander calculation is not invoked because worker exposure would occur only 5 days/week, just as in the Klimisch laboratory animal study.

Thus the subchronic occupational NOEL is calculated as follows:

$$(1700 \text{ ppb}) \times (6 \text{ hr} / 8 \text{ hr}) = 1275 \text{ ppb} = \text{LOEL}$$
$$1275 / 3 = 425 \text{ ppb}$$

The chronic occupational NOEL of 42.5 ppb is estimated by applying the default subchronic-to-chronic uncertainty factor of 10.

IV. Revised occupational seasonal and annual margins of exposure

The recalculated occupational NOELs require that the margins of exposure (MOE) values for occupational scenarios also be recalculated. As such, Table 19 of the 2003 RCD should now read as follows:

Table 19 (*Revised*). Seasonal and annual margins of exposure for occupational scenarios following ground injection or chemigation of metam sodium

		Margins of Exposure		
Site	**Work Task**	**Seasonal[a]**	**Annual[b]**	**n[c]**
A.1 Arizona				
Shank injection	Loader[d]	467	47	10
	Applicator	87	9	2
	Applicator	13	1	4
	Applicator	15	2	4
Solid-set sprinklers	Loader	90	9	10
	Applicator	13	1	10
A.2 Washington State				
Rotary tiller	Loader	429	43	10
	Applicator	23	2	5
	Applicator	30	3	5
Center-pivot sprinklers	Loader	6071	607	5
	Applicator	230	23	5
A.3 Kern Co., CA				
Sprinkler irrigation	Monitor	57	6	1
	Monitors	190	19	4
Shank injection	Irrigators	48	5	3
	Irrigators	113	11	3
	Loaders/applicators	13	1	3
	Loaders/applicators	26	3	3
Inside cab	Breathing zone	24	2	6
A.4 Kern County, CA				
Shank injection	Irrigators	42	4	5
	Loaders/applicators	15	1	3
	Inside cabs	17	2	3

Note: The target MOE for seasonal and annual exposures is 100 for occupational scenarios. This target takes into account uncertainty factors of 10 for interspecies sensitivity and 10 for intraspecies variability.

[a] MOE (Margin of Exposure) = NOEL ÷ occupational task air concentration (from Table 15). Subchronic NOEL = 425 ppb (nasal epithelial atrophy in rats).

[b] Chronic NOEL = 42.5 ppb (nasal epithelial atrophy in rats)

[c] The values for n are exactly those expressed for the 8-hour measurements in Table 13 in the 2003 RCD.

[d] For more precise descriptions of the individual job categories, see footnotes to Table 13 in the 2003 RCD.

V. Revised occupational seasonal and annual RELs

Revised reference exposure levels (RELs) for occupational seasonal / annual scenarios for Table 21 are found below:

Table 21 (*Revised Subchronic and Chronic RELs for Workers*). Summary of definitive studies, regulatory endpoints, critical LOEL and NOEL concentrations, and reference exposure levels (RELs) for airborne MITC

				REL				
Exposure scenario, study	**Endpoint**	**LOEL**	**NOEL**	**1-hr**	**4-hr**	**8-hr**	**24-hr**	**Ref.**
Seasonal[e]	Nasal epithelial atrophy	300 ppb (bystander)	100 ppb (bystander)	----	----	----	1 ppb [a]	Klimisch, 1987
		1275 ppb (occupational)	425 ppb (occupational)	----	----	4 ppb [b]	----	
Annual[e]	Nasal epithelial atrophy	300 ppb (bystander)	10 ppb (bystander)	----	----	----	0.1 ppb[c]	Klimisch, 1987
		1275 ppb (occupational)	42.5 ppb (occupational)	----	----	0.4 ppb[d]	----	

[a] The 24-hr bystander seasonal REL was calculated by estimating the subchronic NOEL from the LOEL and dividing the result by a combined uncertainty factor of 100 (see text).
[b] The 8-hr occupational seasonal REL was calculated by estimating the subchronic NOEL from the LOEL and dividing the result by a combined uncertainty factor of 100 (see text).
[c] The 24-hr bystander annual REL was calculated by dividing the estimated chronic NOEL by an uncertainty factor of 100.
[d] The 8-hr bystander annual REL was calculated by dividing the estimated chronic NOEL by an uncertainty factor of 100.
[e] Based on the rat 4-week subchronic study.