Weight-of-Evidence Evaluation of Methyl Methacrylate Olfactory Effects in Humans and Derivation of an Occupational Exposure Level

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Abstract number 2216
Poster board 414

ABSTRACT

Methyl methacrylate (MMA) causes olfactory effects in rodents. In most cases, these findings are presumptively considered relevant to humans. Recent scientific studies have focused on understanding the apparent lack of species concordance between the rodent and occupational studies. We have applied the Hypothesis-Based Weight-of-Evidence (HBWoE) approach to determine the relevance of the olfactory effects in rodents to humans by evaluating the concordance of the available data and the hypothesis that the observed difference in sensitivity between rats and humans may be the result of physiological and biochemical differences. Our WoE analysis integrated several lines of evidence [animal, human, mode of action (MoA), and toxicokinetics data] and found: 1) acute and chronic rat and mouse MMA inhalation studies consistently indicate degenerative lesions of the main olfactory region as the most sensitive endpoint; 2) numerous studies support an MoA for MMA involving high concentrations of carboxylesterase activity in nasal epithelial tissue that metabolizes MMA to methyl acrylic acid (MAA), an organic acid with irritative and corrosive properties; 3) carboxylesterases are a group of non-specific enzymes that are widely distributed throughout the body in animals and humans; 4) toxicokinetic studies and a physiologically based pharmacokinetic (PBPK) model describing inhalation dosimetry of MMA in the upper respiratory tract (URT) of rats and humans point to differences in nasal morphology and biochemistry that help reconcile these differences as species-specific manifestations of a common toxicological process, and predict a rat-to-human dosimetry adjustment factor (DAF) of 3 to 8, consistent with observed lower sensitivity in humans compared to rats; and 5) worker studies, although somewhat limited, consistently suggest a no observed adverse effect level (NOAEL) for URT irritation, including olfactory dysfunction, of 50 parts per million (ppm). We derived MMA occupational exposure levels (OELs) from the animal data (ranging from 28-118 ppm) and the human data. Overall, our WoE analysis supports use of the human data for derivation of an MMA OEL of 50 ppm.

OBJECTIVE

Our analysis was aimed at developing a robust, science-based recommendation for an occupational standard for MMA that reconciles the rodent and human findings. We employed an HBWoE approach to:

- evaluate the qualitative and quantitative concordance of the available MMA data, and
- consider the hypothesis that the observed difference in sensitivity to MMA between rats and humans is explicable by differences in target-tissue dosimetry that result from physiological and biochemical differences between these species.

BACKGROUND

MMA is a high production volume chemical that is used solely in the manufacture of homopolymers (polymethylmethacrylate) or co-polymers (with other acrylate, methacrylate, or non-acrylic monomers; *e.g.,* styrene, butadiene, or modifiers such as rubber) that are subsequently manufactured into plastic articles and a wide range of industrial, professional, and consumer products.

MMA has been studied extensively over the past 40 years. These studies identified a sensitive lesion in the olfactory epithelium of rats. Because MMA is generally regarded as being of low toxicity, occupational exposure standards for acceptable vapor levels in the workplace have historically been established with regard to worker tolerance of acute irritation of the upper respiratory airways. Recent exposure-standard reviews have been challenged by analyses citing the relatively large amount of rodent inhalation, human experience, and clinical data, and the seeming discordance between exposures causing acute respiratory tract lesions in rats and humans.

METHODS

- We reviewed and interpreted the available toxicological, epidemiological, toxicokinetic, and MoA data for MMA to examine the question of whether rat or human data provide the most robust basis for development of an occupational standard.
- We conducted a WoE analysis, applying our HBWoE approach, to evaluate whether the data are mutually supportive of a common interpretation of MMA inhalation toxicity.
- We incorporated previous work on MMA PBPK and dose-response analyses to derive an occupational standard for MMA.

Table 1 Human MMA NOAELs and LOAELs

Study (exposure type)	Effect	NOAEL	LOAEL
Schwartz *et al.*, 1989 (Chemical manufacturing facility)	Olfactory dysfunction	0.01-56 ppm (EA/AA/MMA mixture)	-
Pausch *et al.*, 1994 (Acrylic sheet production facility)	Eye irritation and lacrimation, pharyngitis, bronchitis, headaches, respiratory or skin sensitization	-	>100 ppm
Muttray *et al.*, 1997 (Acrylic sheet production facility)	Olfactory dysfunction	50 ppm	-
Gosepath *et al.*, 2007 (*In vitro* nasal mucosal culture)	Cytokine release and mRNA induction	<50 ppm	50 ppm
Muttray *et al.*, 2007 (Clinical study)	Cytokine release and mRNA induction, headache, smell	50 ppm	-
van Thriel *et al.*, 2012 (Clinical study)	Nasal airway resistance, nasal mucus biochemistry	Variable concentration gradient (50 ppm average, with 4 peaks at 100 ppm)	-

Notes: EA = ethyl acrylate; AA = acrylic acid; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; - = level not determined; mRNA = Messenger RNA.

RESULTS

Acute and chronic rat and mouse MMA inhalation studies consistently indicate degenerative lesions of the main olfactory region as the most sensitive endpoint (NTP, 1986; Chan *et al.*, 1988; Lomax, 1992).

- From these studies, the lowest observed adverse effect level (LOAEL) for olfactory degeration in rats is 100 ppm; the NOAEL is 25 ppm.
- From these studies, the NOAEL for effects in the nasal respiratory epithelium (inflammation and hyperplasia) in rats and mice is 100 ppm.

Numerous studies support an MoA for MMA involving high concentrations of carboxylesterase activity in nasal epithelial tissue that metabolizes MMA to MAA, an organic acid with irritative and corrosive properties (Bogdanffy *et al.*, 1987; Frederick *et al.*, 1994; Lewis *et al.*, 1994).

- This MoA has been demonstrated for other volatile chemicals, including vinyl acetate (Plowchalk *et al.*, 1997; Bogdanffy and Taylor, 1993) and ethyl acrylate (Frederick *et al.*, 1994; Morris and Frederick, 1995), and it is further supported by studies with the carboxylesterase inhibitor Bis-(p-nitrophenyl) phosphate.
- Carboxylesterases are a group of non-specific enzymes that are distributed widely throughout the body in animals and humans.

Worker studies, although somewhat limited, consistently suggest a NOAEL for URT irritation, including olfactory dysfunction, of 50 ppm (Table 1).

Toxicokinetic studies and a PBPK model describing inhalation dosimetry of MMA in the URT of rats and humans point to differences in nasal morphology and biochemistry that help reconcile rat-human MMA differences as species-specific manifestations of a common toxicological process (Green and Mainwaring, 1996; Thornton-Manning and Dahl, 1997; Bogdanffy *et al.*, 1998; Andersen and Sarangapani, 1999).

- The PBPK model predicts a rat-to-human DAF of 3 to 8 for olfactory effects, consistent with observed lower sensitivity in humans compared to rats.

Some Key Issues/Questions from the WoE Evaluation:

What is known about carboxylesterase activity in hamster olfactory and respiratory nasal epithelium where effects have not been observed?

- Species differences are complex. The possibility of relatively higher dosage rates delivered in the rat compared with the hamster, together with possible toxicodynamic differences in tissue sensitivity, may be responsible for the absence of olfactory lesions in hamsters at 400 ppm MMA (Morris, 1990, 1997; Stott and McKenna, 1985; Trela and Bogdanffy, 1991).

Is carboxylesterase activity found in other parts of the respiratory tract in animals, and what does that mean for potential effects beyond the nose?

- Carboxylesterase activity is found in other parts of the respiratory tract in animals and humans, including the trachea and lungs (where effects have been reported in rats and mice), but only at high concentrations (≥1,000 ppm MMA).

Since rodents are obligate nose breathers and humans are nasal and oral breathers, what is the relevance of lower respiratory tract (LRT) effects observed in humans?

- The data are consistent, with claims by more than one investigator that LRT irritation is associated with high exposures – potentially in excess of 100 ppm.

Are respiratory allergies or asthma reported in humans suggestive of more sensitive effects occurring elsewhere in the human respiratory tract?

- The European Union Risk Assessment Report (ECJRC, 2002) and a review by Borak *et al.* (2011) concluded that there is no convincing evidence that MMA causes asthma.

Table 2 Methyl Methacrylate Occupational Exposure Levels

Value Definition	Rat Studies								Human Studies (NOAEL)
	BMCL for Olfactory Epithelial Effects (Andersen *et al.*, 1999)			US EPA BMCL for Olfactory Epithelial Effects (US EPA, 1998)			DECOS BMCL for Nasal Respiratory Epithelial Effects (Health Council of the Netherlands, 2011)		
Point of Departure (mg/m³)	116	116	116	144	144	144	482	482	205
Dosimetric Adjustment Factor (DAF)[1,2]	3	3	8	3	3	8	none	none	none
Interspecies Uncertainty Factor (UF)[1,2]	1	1	3	1	1	3	1	1	none
Intraspecies Uncertainty Factor (UF)[1,2]	3	1	1	3	1	1	3	1	none
Occupational Level (mg/m³)	116	348	309	144	432	384	161	482	205
Occupational Level (ppm)	28	85	76	35	106	94	39	118	50

Notes: 1 ppm = 4.09 mg/m³; BMCL = benchmark concentration lower confidence limit; DECOS = Dutch Expert Committee on Occupational Safety.
(1) The point of departure is multiplied by the DAF (comparable to how US EPA applies the regional gas dose ratio) and divided by the UFs.
(2) The DAF reflects toxicokinetic differences between rats and humans. The UFs represent toxicodynamic differences between rats and humans (interspecies UF) and within the human population (intraspecies UF).

We derived MMA OELs from animal and human data starting with three BMCL (95% Lower Confidence Limit on the Benchmark Concentration) values (Table 2).

Interspecies Uncertainty Factors (UF)

- Olfactory Effects: A UF for toxicodynamic differences between rats and humans is considered unnecessary when applying the conservative DAF of 3. We applied a UF of 3 when using the less conservative DAF of 8.
- Nasal Respiratory Effects: A DAF of 1 and UF of 1 for interspecies toxicodynamic differences was applied to the Dutch Expert Committee on Occupational Safety (DECOS) BMCL.

Intraspecies UFs ranged from 1 to 3 to account for variability among humans in a worker population beyond the limited variability within the test animal population.

Example Calculations

116 mg/m³ x 3 (DAF) ÷ 1 (interspecies UF) ÷ 3 (intraspecies UF) = 116 mg/m³ = 28 ppm
144 mg/m³ x 3 (DAF) ÷ 1 (interspecies UF) ÷ 3 (intraspecies UF) = 144 mg/m³ = 35 ppm
482 mg/m³ x 1 (DAF) ÷ 1 (interspecies UF) ÷ 3 (intraspecies UF) = 161 mg/m³ = 39 ppm

CONCLUSION

- When appropriate adjustment factors (DAFs and UFs) are applied to the rodent-derived BMCLs, the resulting exposure levels (28-118 ppm) are very similar to the human NOAEL and proposed OEL of 50 ppm.
- Overall, our WoE analysis supports use of the human data for derivation of an MMA OEL of 50 ppm.
- Typical MMA exposure levels today are well below 50 ppm.

ACKNOWLEDGEMENT

The underlying work for this poster was supported by the Methacrylate Producers Association, Inc.