Regulatory Toxicology and Pharmacology 66 (2013) 217–233

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Hypothesis-based weight-of-evidence evaluation of methyl methacrylate olfactory effects in humans and derivation of an occupational exposure level ☆

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ARTICLE INFO

Article history:
Received 1 November 2012
Available online 11 April 2013

Keywords:
Methyl methacrylate
Olfactory effects
Human relevance
Occupational levels
Physiologically based pharmacokinetic (PBPK) model
Dosimetric adjustment factors

ABSTRACT

Over 40 years of scientific evidence indicates that methyl methacrylate (MMA) causes olfactory effects in rodents that are relevant to humans. More recent scientific studies have focused on understanding the apparent lack of species concordance between the rodent and human studies. 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 could explain and reconcile these differences as species-specific manifestations of a common toxicological process. We have applied the hypothesis-based weight-of-evidence (HBWoE) approach to evaluate the concordance of the available data and the hypothesis that the observed difference in sensitivity between rats and humans may be the expected result of physiological and biochemical differences. Our WoE analysis indicates that when the several lines of evidence (i.e., animal, human, mode-of-action, and toxicokinetics data) are integrated, they inform interpretation of one another and, overall, support use of the human data for derivation of an MMA occupational exposure level (OEL) of 50 ppm.

1. Introduction

Methyl methacrylate (MMA) is a high production volume chemical that has been in commerce for over 65 years and is used solely in the manufacture of acrylic-based homopolymers (polymethylmethacrylate) or co-polymers. These polymers are subsequently manufactured into plastic articles, as well as a wide range of industrial, professional, and consumer products. Relatively small quantities of liquid MMA are used in some skilled-trade, medical, dental, and hobbyist products.

MMA has been studied extensively over the past 40 years. Several comprehensive reviews have been conducted, including the European Union's (EU) Existing Substances Risk Assessment (CEC, 1993), the Organisation for Economic Co-operation and Development's Screening Information Dataset (OECD, 2003), and, more recently, the registration of MMA under the EU's Registration, Evaluation, Authorisation and Restriction of Chemicals regulation (EC, 2006). In the 1970s, considerable research was conducted on MMA, including a range of repeat-dose studies (NTP, 1986; Chan et al., 1988; IARC, 1994; Hazelton, 1979a, 1979b; Lomax, 1992). These studies identified a sensitive lesion in the olfactory epithelium of rats that was subsequently studied in depth. 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. More recent exposure-standards 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. On the other hand, toxicokinetic studies and a physiologically based pharmacokinetic (PBPK) model for MMA in the upper respiratory tract (URT)

Abbreviations: 2-EH, 2-ethyl Hexanol; AA, acrylic acid; ACGIH, American Conference of Governmental Industrial Hygienists; BMCL, benchmark concentration lower confidence limit; BNPP, bis-(p-nitrophenyl) phosphate; DAF, dosimetric adjustment factor; DECOS, Dutch Expert Committee on Occupational Safety; EA, ethyl acrylate; ELISA, enzyme-linked immunosorbent assays; EU, European Union; GM-CSF, granulocyte-macrophage colony-stimulating factor; HBWoE, hypothesis-based weight-of-evidence; LC_{50}, lethal concentration 50; LOAEL, lowest observed adverse effect level; LRT, lower respiratory tract; MAA, methacrylic acid; MMA, methyl methacrylate; NOAEL, no observed adverse effect level; NPSH, non-protein sulfhydryl; NTP, National Toxicology Program; OECD, Organisation for Economic Co-operation and Development; OEL, occupational exposure level; PBPK, physiologically based pharmacokinetic; PCR, polymerase chain reaction; RfC, reference concentration; SO, septal organ; TLV, threshold limit value; TWA, time-weighted average; UF, uncertainty factor; UPSIT, University of Pennsylvania Smell Identification Test; URT, upper respiratory tract; US EPA, United States Environmental Protection Agency; VA, vinyl acetate; WoE, weight-of-evidence.

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http://dx.doi.org/10.1016/j.yrtph.2013.04.001

(comprising the nose, nasal cavity, ethmoidal air cells, sinuses, larynx, and trachea) of rats and humans point to species differences in URT morphology and biochemistry that could explain these differences. We have therefore undertaken a weight-of-evidence (WoE) approach to evaluate the qualitative and quantitative concordance of the available data, and to consider the hypothesis that the observed differences in sensitivity between rats and humans are explicable by differences in target-tissue dosimetry that result from physiological and biochemical differences between these species. Our analysis is aimed at developing a robust, science-based recommendation for an occupational standard for MMA that reconciles the rodent and human findings. We have intentionally not addressed compliance and socio-economic aspects that might be considered during the setting of a regulatory standard.

The hypothesis-based weight-of-evidence (HBWoE) approach we employ stresses that when using effects seen in animals as evidence for potential effects in humans, one is invoking the hypothesized commonality of the agent's potential actions across settings. The animal experiments constitute evidence because they raise the possibility that, owing to fundamental mammalian similarities in anatomy, physiology, and biochemistry, the reactions to exposure observed in animals would be paralleled in humans. The evidence for qualitative hazard in humans improves to the extent that this presumed commonality across species in the basic causative biological processes can be experimentally confirmed to operate consistently across settings. Confidence in the characterization of exposure-dependent toxicity is enhanced to the degree that it can be shown to be quantitatively (not just qualitatively) consistent across species and exposure regimens once one has examined and allowed for the patterns of quantitative differences in dosimetry. Breathing rates, airflows, and metabolic activity affect the relative target-tissue exposures in animals and humans for a given air concentration inhaled. Since animal and human observations appear to show the same causal processes producing toxicity, and allowing for known quantitative differences in these determinants makes exposure–effect relationships consistent across species and dosing regimens, one can base the characterization of exposure limits on comprehensive data, rather than choosing one or another dataset as the basis. Establishing this generality of causative processes makes the determination more rigorous, decreases the concern about which particular dataset was chosen to set a standard, and overcomes doubt about potential uncertainties associated with any one dataset.

We have followed this approach in the present analysis. Accordingly, we proceed by stepping through the various sources of data, asking specific questions about data quality, whether the data should be considered dependable and consistent among available studies, and whether the consistency of causative processes indeed seems to hold across dosing regimens and species. We first consider MMA inhalation toxicity in the setting of acute, sub-acute, sub-chronic, and chronic animal exposure studies. The apparent determinants of toxicity in these settings, including the role of the uptake and metabolism, are then reviewed with what is known about animal-human differences in these processes. We take into account the available data from humans and ask whether this experience is indeed consistent with the notion of common underlying causes of toxicity across rodents and humans. Finally, we consider alternatives that have been put forth for development of recommended limits to human exposure that would be based on the various sources of data, showing that they are consistent when allowances for pharmacokinetics are made. In fact, considering the obvious differences between rodent and human nasal morphology and breathing patterns, it is not surprising that the PBPK model predicts significant differences between rodents and humans. Further, extrapolation of animal-to-human effects based on the PBPK model yields toxicity values very similar to those derived from the human data. We conclude that a standard based on actual observations of workers forms the best basis. The robustness of this standard is supported by considering how it is consistent with a common toxicity-generating process and pattern of exposure dependence across human and animal studies.

2. Materials and methods

We conducted a literature search in PubMed, Scopus, Toxline, and EMBASE using combinations of the following terms: methylmethacrylate, methyl methacrylate, animals, humans, toxicity, toxicology pharmacokinetics, PBPK, mechanisms, mode of action, toxicokinetics, metabolism, absorption, uptake, distribution, elimination, excretion, dose, dosimetry, dose–response, models, modeling, computational fluid dynamics, inhalation, inhaled, nasal, nose, respiratory, olfactory, rhinitis, vapor, vapour, air, and occupational. Titles and abstracts of the search results were reviewed to identify key studies in support of the MMA WoE analysis. We narrowed the results to relevant publications that focus on the following:

- inhalation exposures or respiratory tissues; studies using other routes (e.g., intravenous, subcutaneous, dermal, or oral) were excluded;
- endpoints of the respiratory system, nasal passages, olfactory system, lungs, and bronchial system;
- mammalian species and humans; other species were excluded;
- MMA metabolism and mode of action; and
- MMA inhalation dosimetry and PBPK modeling.

We also reviewed the United States Environmental Protection Agency's (US EPA) Toxicological Profile for MMA (US EPA, 1998) and the recent MMA Health-Based Recommended Occupational Exposure Limit document (Health Council of the Netherlands, 2011) for additional relevant documents.

We reviewed and summarized the selected studies and applied a modified version of our HBWoE approach. This focuses predominantly on overall study quality and relative consistency within and across various lines of evidence, asking several questions that should be considered in extrapolating results in rodents to potential human risk. The specific HBWoE evaluation approach is described in more detail in our recent publications (Rhomberg et al., 2010, 2011; Prueitt et al., 2011).

The results of the WoE analysis were further considered in deriving an occupational exposure level (OEL) for MMA.

3. Studies in animals

3.1. Acute studies

The acute systemic toxicity of MMA by the inhalation route is low, as indicated by several studies conducted before the establishment of OECD guidelines, reporting a lethal concentration 50 (LC_{50}) (4-h) of greater than approximately 6000 ppm (25 mg/L) in rats (Tansy et al., 1980a). Systemic effects were not well documented and, where mentioned, tended to be non-specific in nature, with depression, ataxia, and excessive salivation being reported in mice (Spealman et al., 1945). Local effects in the form of lesions in the olfactory region of the nasal cavity were observed following acute (6-h) inhalation of MMA in F344 rats at 200 ppm (948 mg/m^3) (Jones, 2002). Comparable lesions were also observed in the main olfactory region (turbinates) of the nasal cavity, as well as the organ of Rodolfo Masera (a small island of olfactory epithelium, surrounded by respiratory epithelium, lying near the ventral base of the nasal septum at the entrance to the nasopharynx of some