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METHACRYLATE PROD ASSOC INC		
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SUPPORT: LTR FR MPA TO USEPA W/ADDTNL INFO RE AN ACUTE INHALATION TOX STDY OF ETHYL & METHYL METHACRYLATE IN RATS (8EHQ-0401-14894), AS REQST'D BY USEPA, DTD 101101		
Chemical Category		
ETHYL METHACRYLATE & METHYL METHACRYLATE		

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8EHQ-1101-14894



8EHQ-01-14894

October 11, 2001

Document Control Office (7407)
Room G99 East Tower Attn: Section 8(e)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460-0001

Contain NO CBI

Subject: 8EHQ-0401-14894

Dear Mr. Terry O'Bryan:

I am writing in response to a letter from Richard Hefter, EPA, in which he requested additional information regarding the cited TSCA Section 8(e) submission made on April 4, 2001. I have listed below some additional information regarding this study.

The study was conducted with 5 male F344 rats with bodyweights between 265-295 grams. The rats were exposed to 200 ppm of ethyl methacrylate for a period of 6 hours. The rats were killed immediately after exposure with halothane and the heads processed exactly as described for methyl methacrylate in previous studies.

The nasal tissue of rats exposed to ethyl methacrylate showed slight to moderate degeneration of the olfactory epithelium lining the central septum and mid ethmo-turbinates. The effects were similar in appearance and distribution to those observed for methyl methacrylate (CAS No. 80-62-6). The respiratory mucosa throughout the nasal passages and the olfactory mucosa in regions adjacent to these areas were not affected by exposure to ethyl methacrylate. These data were presented at the last SOT meeting and the Abstract is attached.

As indicated in our April submission, we do not believe that these findings represent a significant risk for humans. This research was conducted as part of a PhD project and therefore the data would not be issued as a final report.

This submission is being made on behalf of the MPA member companies: CYRO Industries, ATOFINA Chemicals, Inc., Ineos Acrylics, Inc., and Rohm and Haas Company. Nothing in this letter is considered confidential business information of MPA or its members.

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T. O'Bryan, EPA
October 11, 2001
Page 2

If you have any questions regarding this submission, please contact me.

Sincerely,

A handwritten signature in black ink, appearing to read "Elizabeth K. Hunt". The signature is stylized and cursive.

Elizabeth K. Hunt
Executive Director

Society of Toxicology.

40th Annual Meeting

**An Official Journal of the
Society of Toxicology
Supplement**

TOXICOLOGICAL SCIENCES
Formerly Fundamental and Applied Toxicology

The Toxicologist

Abstracts of the 40th Annual Meeting.

Oxford University Press

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models was accomplished using published data. Metabolic interactions within the chemical mixture (i.e., competitive inhibition) were described using kinetic constants estimated *in vivo*. Elevated TCE blood levels as a result of metabolic inhibition were used as indicator of chemical interactions, and interaction thresholds were calculated at different significance levels. Simulated TLV exposures to the three solvents revealed a significant increase in the TCE blood concentration (14%) as compared to single chemical exposure. Assuming 10% change of TCE blood level is a significant health effect, interaction threshold for the ternary mixture of TCE, PERC and MC was calculated at 50, 25, and 190 ppm respectively. TLV exposure to binary TCE/PERC mixtures did not affect significantly the pharmacokinetics of the either compounds, while interaction threshold for TCE/MC co-exposure was reached at 50 and 240 ppm respectively. The interaction threshold concept illustrates the potential application of PBPK modeling in the process of risk assessment of occupational and environmental exposure to chemical mixtures. This study was supported by ATSDR (Cooperative Agreement U61/ATU881475), and NIEHS Superfund Basic Research Program (P42 ES05949).

710 PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL FOR HUMAN EXPOSURE TO METHYL TERTIARY-BUTYL ETHER.

T. L. Levens¹, D. L. Ashley², J. D. Pleil¹, M. W. Case¹ and J. D. Emb¹. ¹USEPA, Research Triangle Park, NC and ²Center for Disease Control and Prevention, Atlanta, GA.

Humans can be exposed by inhalation, ingestion, or dermal absorption to methyl tertiary-butyl ether (MTBE), an oxygenated fuel additive, from contaminated water sources. The purpose of this research was to develop a physiologically based pharmacokinetic model describing the disposition of MTBE and the metabolic tertiary butyl alcohol (TBA) from inhalation, oral, and dermal exposures. Compartments in the model included alveolar space, arterial and venous blood, brain, fat, gastrointestinal tract, kidney, liver, rapidly perfused tissues, muscle and exposed skin, and slowly perfused tissues. To accurately simulate the clinical human exposure and sampling conditions, the exposed arm and sampled arm were described by subcompartments for arterial blood, upper arm veins, forearm tissue, forearm skin, antecubital venous blood, and venous blood. Metabolism of MTBE and TBA was assumed to occur only in the liver, and elimination of TBA was assumed to occur via exhalation of MTBE and TBA and urinary elimination of TBA. Dermal absorption was described by Fick's law, and oral absorption was described as first order for the bioavailable dose. Initial estimates for parameters were obtained from the literature. Assuming that the physiological and biochemical parameters did not vary among the three routes of exposure, final estimates for parameters in the model were obtained by comparing the model with data for blood and alveolar breath concentrations of MTBE and TBA in male subjects who were exposed by inhalation, ingestion, or skin absorption. The model with the optimized parameters accurately simulated pharmacokinetics of MTBE and TBA in humans for all three routes. Of the inhaled, oral, and dermal doses 54, 47, and 54%, respectively, were exhaled as MTBE, and 44, 52, and 44%, respectively, were metabolized to TBA. This model can be used to simulate environmental exposure to MTBE. (This is an abstract of a proposed presentation and does not necessarily reflect EPA policy).

711 PREDICTING THE BIOLOGICAL FATE OF METHACRYLATE ESTERS IN RATS AND HUMANS USING PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING.

O. Jovan^{1,2}, T. Green¹ and B. Houston². ¹Zeneca Central Toxicology Laboratory, Investigative Toxicology Section, Macclesfield, United Kingdom and ²University of Manchester, School of Pharmacy and Pharmaceutical Sciences, Manchester, United Kingdom. Sponsor: E. Loch.

The alkyl methacrylate esters are high volume chemicals which are hydrolysed in the body by carboxylesterases to methacrylic acid (MAA), an irritant/corrosive. Carboxylesterases are distributed within many tissues, and there is a concern that MAA could accumulate and cause tissue damage local to ester metabolism in humans exposed to these compounds. The biological fate of a series of methacrylates (C_2 to C_{12}), has been investigated, firstly in the rat and secondly in man, using a combination of physiologically based pharmacokinetic modelling (PB-PK) and a limited number of *in vivo* experiments carried out in the rat. The toxicokinetic processes that the methacrylate esters undergo *in vivo*, namely partition coefficients and absorption & metabolic rate constants have been measured using both human and rat tissue *in vitro*. Those partition coefficients measured using rat tissues include blood-air which range from, 50-950; fat-blood, 14-200 and liver-blood where

values less than 10 were measured. The intrinsic clearance by whole rat blood of 7 esters from methyl to octylMAA (C_2 to C_7) was measured and they were found to increase with molecular volume from 4.6-34.0 $\mu\text{L}/\text{min}/\text{kg}$. In contrast, human blood ranged from 1.5-5.2 $\mu\text{L}/\text{min}/\text{kg}$, with butylMAA showing the most rapid and octylMAA the least rapid hydrolysis. The intrinsic clearance in the rat liver ranged from 2.7-20.6 $\mu\text{L}/\text{min}/\text{kg}$ (C_2 to C_7), compared to 0.3-5.0 $\mu\text{L}/\text{min}/\text{kg}$ in the human liver. *In vivo* experiments in the rat, have shown that the systemic clearance of both MAA and esters (up to C_7) is very rapid ($t_{1/2} < 5$ min), these data are in close agreement with model simulations. The very rapid clearance of MAA in the rat suggests that toxicity arising from a systemic accumulation of this metabolite is unlikely.

712 A PHARMACOKINETIC MODEL FOR ARSENIC METABOLISM IN PRIMARY RAT HEPATOCYTES.

M. R. Easterling¹, M. Seybo², M. V. Evans² and E. M. Kenyon³. ¹University of North Carolina, Curriculum in Toxicology, Chapel Hill, NC. ²University of North Carolina, Department of Pathology, School of Medicine, Chapel Hill, NC and ³USEPA, NHEERL, ORD, Pharmacokinetics Branch, Research Triangle Park, NC.

Arsenic is a known human carcinogen and widespread contaminant in drinking water. A pharmacokinetic model describing the uptake and methylation of arsenite (AsIII) in primary hepatocytes was developed as part of a larger effort to develop a physiologically-based pharmacokinetic model for arsenic (As) metabolism. Measured metabolites were As, mono-methylated As (MMA), and di-methylated As (DMA) in both cells and media. Time course data for AsIII, MMA, and DMA at three initial media AsIII concentrations (0.1, 0.4, 1.0 μM) were used to estimate the transport and methylation parameters. This model incorporates the sequential enzymatic methylation of arsenite to MMA and DMA via first order and Michaelis-Menton kinetics, respectively. Uncompetitive inhibition of the formation of DMA by AsIII was also incorporated on the basis of previous work showing an increased time lag in the production of DMA at higher concentrations of arsenite that resulted in decreased amounts of DMA being formed. Transport of AsIII into the cell was modeled as a saturable process and binding of arsenite to proteins within the cell was also included, as were efflux of MMA and DMA from the cell. The large number of model parameters estimated from the data made sensitivity analysis critical in determining parameters for which independent estimates are needed. Sensitivity analysis showed the transport parameter for AsIII and DMA out of the cell to be critical, suggesting the need for experimental studies of efflux. This hepatocyte model will contribute to the development of a model for human hepatocytes and aid in the design of additional studies using human hepatocytes. (This abstract does not reflect EPA policy.)

713 DOSE-RESPONSE MODELING OF HEPATIC PROTEIN INDUCTION IN RATS EXPOSED TO INHALED OCTAMETHYLCYCLOTETRAILOXANE (D4).

K. P. Florke¹, R. Swarnapani², J. Teegarden², J. M. McKim¹ and J. E. Anderson¹. ¹Dow Corning Corporation, Health and Environmental Sciences, Midland, MI. ²The K.S. Crump Group, Research Triangle Park, NC and ³Colorado State University, Department of Environmental Health, Ft. Collins, CO.

As part of an ongoing risk assessment effort to develop biologically based dose-response models for D4, a pharmacodynamic model was developed that describes total and regional hepatic induction of CYP2B1/2 and high-dose inhibition of CYP2B1/2 activity by D4. Inhalation exposure by rats produces CYP2B1/2 protein induction, increased liver weight, cell hypertrophy, and increases in cell proliferation. These responses are similar to those observed following exposure to phenobarbital (PB). Single and five-compartment liver models were developed to simulate D4-mediated hepatic induction of CYP2B1/2 protein in female F344 rats following 6 hr/day, 5 day inhalation exposures to 0, 1, 7, 30, 70, 190, 300, 500, 700 or 900 ppm D4. Each model provided good fits to plasma, liver and fat D4 concentrations, and to hepatic PROD activity following inhalation exposure to D4. With the single compartment liver model, optimized values for the composite K_d and Hill coefficient, N , for induction were 0.67 μM and 1.9. Comparable values reported for PB are 10 μM and 1.7. The K_d for induction of CYP2B1/2 by D4 is 15 fold lower than for PB. To describe regional differences in induction a 3-compartment model was used with Hill coefficients of 4.0. Different values of the Hill coefficient between the single ($N=1.7$) and five ($N=4$) compartment liver models resulted in different low-dose non-linearities in the dose-response for hepatic CYP2B1/2 induction. The ED01 predicted by the 1 and 5 compartment models was 2.1 and 5.1 ppm, respectively. The use of this pharmacodynamic model describing protein induction and inhibition in conjunction with a pharmacokinetic model describing tissue dosimetry has increased our understanding of the low-dose behavior of the hepatic system to D4.

8EHQ-0401-14894

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METHACRYLATE PRODUCERS ASSOCIATION, INC.

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Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
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Washington, DC 20460

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Subject: TSCA 8(e) Submission - Ethyl Methacrylate (CAS No. 97-63-2)

Dear Sir/Madam:

The Methacrylate Producers Association, Inc. (MPA) is submitting results of an investigative study on the uptake, disposition and nasal toxicity in rats to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e). The study provides information on ethyl methacrylate and does not involve effects in humans.

This submission is being made on behalf of the MPA member companies: CYRO Industries, ATOFINA Chemicals, Inc., Ineos Acrylics, Inc., and Rohm and Haas Company. Nothing in this letter is considered confidential business information of MPA or its members.

The uptake, disposition and nasal toxicity of ethyl methacrylate, as well as several other methacrylate esters, were examined in test groups of five rats at a dose level of 200 ppm. The nasal tissue of rats exposed to ethyl methacrylate showed slight to moderate degeneration of the olfactory epithelium lining the central septum and mid ethmo-turbinates. The effects were similar in appearance and distribution to those observed for methyl methacrylate (CAS No. 80-62-6). The respiratory mucosa throughout the nasal passages and the olfactory mucosa in regions adjacent to these areas were not affected by exposure to ethyl methacrylate.

While we do not believe that these findings represent a significant risk for humans, this is to our knowledge the first report of such effects in rats.

If you have any questions regarding this submission, please contact me at (703) 327-6276 or via e-mail at ehunt@loudoun.com.

Sincerely,

Elizabeth K. Hunt / MPA

Elizabeth K. Hunt
Executive Director

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

**OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES**

April 26, 2001

Methacrylate Producers Association, Inc.
Attn: Elizabeth K. Hunt
Executive Director
1250 Connecticut Avenue, N.W., Suite 700
Washington, DC 20036

SUBJECT: 8EHQ-0401-14894

Dear TSCA 8(e) Submitter:

As part of EPA's responsibility to evaluate and publicize TSCA 8(e) submissions, the Office of Pollution Prevention and Toxics conducts preliminary screens of all 8(e) and routinely requests additional information from submitters to complete this preliminary screen. Please provide a copy of the final report from the ethyl methacrylate study summarized in your 8(e) submission. If the final report is not yet available, please provide information on the dosing schedule followed in this study and any additional information relating to study protocol and test results.

Enclosed is the first page of your submission and a copy of "Support Information for Confidentiality Claims". Please cite the assigned 8EHQ number and address your response to:

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Room G99 East Tower Attn: Section 8(e)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460-0001

Questions regarding this request should be directed to Mr. Terry O'Bryan of my staff at (202) 260-3483 or E-Mail OBRYAN.TERRY@EPA.GOV

Sincerely,

Richard H. Hefter, Chief
High Production Volume Chemicals Branch

Enclosures