



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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

AUG 25 2005

Mr. William P. Gulledge
Ketones Panel Manager
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22205

Dear Mr. Gulledge:

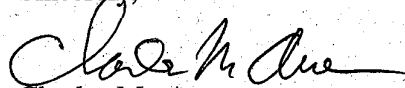
Thank you for coordinating the Ketone Panel's sponsorship and assessment activities regarding methyl ethyl ketone (MEK) in EPA's Voluntary Children's Chemical Evaluation Program (VCCEP). EPA truly appreciates the contributions of the Panel and its member companies, Celanese, ExxonMobil Chemical Company, Shell Chemical Company and E.I. du Pont de Nemours & Co., to VCCEP. This letter is to alert the Ketone Panel and its member companies to EPA's VCCEP Tier 2 Data Needs Decision for MEK. In formulating this decision, EPA has considered all available information including assessments provided by the Ketone Panel and the results of the VCCEP MEK Peer Consultation.

EPA concurs that there are sufficient Tier 1 toxicology and exposure information on MEK to characterize risks to children. EPA has not identified any VCCEP Tier 2 data needs for MEK which is consistent with the conclusions of the Peer Consultation. EPA, however, did identify several deficiencies in the initial Tier 1 assessment. The Ketone Panel addressed these concerns by the submission of supplemental information, dated January 12, 2005, to the Agency.

EPA's Data Needs Decision document, along with this letter, will be posted on the VCCEP website so that other stakeholders are informed of the status of MEK in the VCCEP. EPA notes that this decision is specific for MEK and does not set a precedent for future VCCEP cases.

Please contact Linda Gerber, the Acting Associate Director of the Chemical Control Division in EPA's Office of Pollution Prevention and Toxics if you have any questions or concerns associated with this Data Needs Decision. Ms. Gerber can be reached at (202) 564 - 3452.

Sincerely,

A handwritten signature in cursive script, appearing to read "Charles M. Auer".

Charles M. Auer

Director

Office of Pollution Prevention and Toxics

**VOLUNTARY CHILDREN'S CHEMICAL
EVALUATION PROGRAM:
DATA NEEDS DECISION DOCUMENT
OF METHYL ETHYL KETONE**

Prepared By
Risk Assessment Division (7403M)
Office of Pollution Prevention & Toxics
April 11, 2005

Table of Contents

Preface	ii
1.0 Summary of EPA Recommendations for VCCEP Tier 2 Data Needs	1
2.0 Summary of Tier 1 Exposure Assessment	1
3.0 Summary of Tier 1 Hazard Assessment	6
4.0 Summary of Tier 1 Risk Characterization	14
5.0 Summary of Sponsor's Tier 2 Data Needs	20
6.0 EPA Response to the Sponsor's Tier 2 Data Needs	21

Preface

Chemicals of potential concern to children's health are the subject of evaluation in the pilot Voluntary Children's Chemical Evaluation Program (VCCEP). VCCEP was developed to ensure that there are adequate publicly available data to assess the impact that industrial chemicals may have on children.

In August 1999, OPPT announced the initiation of a process in which it sought stakeholder input on all aspects of the VCCEP. OPPT held three public meetings and took comments on possible designs for a voluntary program. After considering all the comments of interested stakeholders, the pilot VCCEP was announced in a *Federal Register* notice on December 26, 2000. In the notice, OPPT asked companies that produce and/or import 23 specific chemicals to volunteer to sponsor their evaluation in Tier 1 of a pilot of the VCCEP. Thirty-five companies and ten consortia responded and volunteered to sponsor 20 of the chemicals.

The ultimate objective of the VCCEP is to ensure that there are adequate toxicity and exposure information available to assess the potential risks to children. A tiered approach is being pursued to gather the information, with each subsequent tier, of the three tiers, including more complex toxicology and exposure studies. Information from all three tiers may not always be necessary to adequately characterize the risk to children. The sponsor develops a chemical assessment at each tier of analysis. The assessment includes four sections: a summary of the toxicology information, a summary of the exposure information, a risk characterization, and a data needs assessment. The data needs assessment discusses the need for additional data, which could be provided by the next tier, to fully characterize the risks the chemical may pose to children.

During the public stakeholder meetings, it was proposed that an outside group of scientific experts should have the opportunity to provide comments on the data needs portion of the assessments. The approach adopted involves convening a group of scientific experts with extensive and broad experience in toxicity testing and exposure evaluations, as well as expertise in the specific chemical, referred to as a Peer Consultation Panel. The sponsor provides the assessments to an outside third party who is responsible for seeking input through the Peer Consultation Panel. The outside third party develops a summary of the panel's opinions and makes it available to the sponsor and the public.

OPPT reviews the sponsor's assessment and develops a response to the sponsor specifically on the data needs assessment. The response focuses primarily on whether any additional information is needed to adequately characterize the potential risks to children. EPA's response is sent to the sponsor and made available to the public.

Additional information regarding the Voluntary Children's Chemical Evaluation Program is provided in Appendix A and is available at <http://www.epa.gov/oppt/chemrktk>.

In April 2003, the American Chemistry Council's Ketones Panel submitted its Tier 1 assessment of methyl ethyl ketone (MEK) for the Voluntary Children's Chemical Evaluation Program (VCCEP). OPPT has reviewed the four components of the assessment, and where appropriate, has confirmed the accuracy of the toxicology and exposure information. EPA has recently independently reviewed the available toxicology information as part of its IRIS program. This assessment has been extensively peer reviewed and was published in September, 2003. As part of a petition to delist MEK from the list of hazardous air pollutants (HAPs), EPA conducted another review of the available toxicology information on MEK. EPA also reviewed the report of the peer consultation panel that provided comments on the assessment; this report is available at www.tera.org. Finally, EPA reviewed a January, 2005 letter from ACC to EPA on behalf of the sponsors regarding three exposure issues: 1) Exposure Considerations for Prospective Parents; 2) Daily Exposure Aggregates; and 3) TLV Use to Calculate Exposure to Nursing Infants.

1.0 Summary of EPA Recommendations for VCCEP Tier 2 Data Needs

1. EPA agrees that all tier 1 exposure analyses have been conducted, based on its review of the original submission and the January 2005 letter from ACC to EPA. For VCCEP, EPA does not recommend any tier 2 exposure studies.
2. EPA agrees that all tier 1 toxicology studies have been conducted. EPA also notes that most tier 2 toxicology studies have been conducted. EPA does not recommend additional tier 2 studies for VCCEP at this time.

2.0. Summary of Tier 1 Exposure Assessment

Production, Applications and Fate

The sponsor's submission states that global MEK production capacity in 1999 was approximately 2.34 billion pounds and domestic production was 572 million pounds. The sponsor's submission indicates that each of the three companies that produce MEK does so at a single facility. Two facilities are in Louisiana; the third is in Texas.

The sponsor's submission discusses MEK, an industrial and commercial product, providing a production volume, a list of uses, and the percentage of production used in different broadly defined use categories, such as adhesives and coatings. The sponsor's submission also presents emission volumes to air, water, and land for facilities using MEK as well as production facilities. The tables presenting emissions data for facilities using MEK provide a number of facilities and a percentage value for various ranges of emissions, e.g., 1 to 10,000 lbs/year, 10,001 to 100,000 lbs/year, etc. Two facilities release between 1 million and 10 million lbs/year. These two facilities may account for as much as half of the total air emission for the 1,778 facilities for which data are available.

According to the sponsor's submission, MEK is widely used in surface coatings, adhesives, printing inks, magnetic tapes, and lube oil dewaxing agents. It is also used as an intermediate in the manufacture of other chemicals. Consumer products containing MEK include automotive products, such as carburetor cleaner, auto body polishes, gasket adhesive removers, auto paint and primer, transmission cleaner, and tire cleaner; household cleaners, such as metal polishes and floor wax; paint-related products, such as spray paint, paint thinner, paint remover, and wood stain; cleaning products, including spot removers; cleaning solvents for tape heads and other electronic devices; lubricants; and adhesives, including glue used in the assembly of models by hobbyists.

The production volume was not used to derive values for concentrations of MEK in the environment; these values were instead derived from monitoring studies. Concentrations in

consumer products were derived through the use of publicly available product databases and product data sheets.

According to the sponsor's submission, MEK is expected to exist solely as a vapor in the ambient atmosphere, based upon its vapor pressure. MEK is soluble in water but will evaporate from water surfaces based upon a Henry's Law constant of $4.7 \times 10^{-5} \text{ atm}\cdot\text{m}^3/\text{mol}$ at 25° C . Volatilization is expected to be rapid, with an estimated river half-life of 15 hours. MEK will volatilize from both dry and wet soils, based upon its vapor pressure and Henry's Law constant, respectively.

According to the sponsor's submission, MEK is biodegraded in the environment under both aerobic and anaerobic conditions. It is not expected to sorb in sediment or suspended matter or soil, based upon a log octanol-water partition coefficient of 0.29. These properties indicate that MEK is not persistent, and potential for bioconcentration via the food chain is not an issue.

According to the sponsor's submission, the physical-chemical properties of MEK indicate that under environmental conditions, air and water are potential pathways for MEK exposure, but soil is not likely to be a significant pathway.

MEK is present in many foods, usually as a naturally-occurring chemical, but occasionally as a food additive. MEK may occur as a metabolic product in the human body or as a naturally-occurring compound in foods and beverages, especially those that undergo microbial transformation, such as cheese and alcoholic beverages.

Occupational Exposure

For occupational exposures, the sponsor considered ingestion of breast milk from an occupationally exposed mother as the exposure pathway of most significance to children. The sponsor did not consider transfer via adherence to parental skin or clothing as a pathway for MEK, due to its volatility; any MEK on skin or clothing surface should evaporate before reaching home given that the evaporation rate of a 0.01 cm thick film of MEK is 43 seconds based upon a vapor pressure of 91 mm Hg at 25° C .

The sponsor's assessment concluded that MEK can partition into breast milk, but it is not expected to bioconcentrate due to its rapid metabolism and elimination from the body. The sponsor's assessment also concluded that the MEK octanol water partition coefficient does not predict significant bioconcentration in lipids.

The potential infant exposure to MEK via breast milk of an occupationally exposed mother was estimated by the sponsor using the analysis presented in Fisher et al. (1997). The sponsor considered the assumptions in this study to be conservative such that the results are an

upper bounding estimate of infant exposure (i.e., an estimate that falls above the expected exposure range). According to the sponsor, the mother was assumed to be exposed to a constant concentration at the TLV (200 ppm) throughout the workday and the infant was assumed to be nursed at intervals throughout the work period with each nursing bout assumed to start 6 minutes after the occupational exposure stopped. The infant was further assumed to ingest a total of 920 ml during a 24 hour day, with 8 feedings of 115 ml each (whereas lactating women on average produce 680-840 ml breast milk/day and infants average 7-8 feedings per day).

This resulted in a predicted exposure estimate of 12.08 mg MEK/day for a nursing infant. The sponsor considered the milk intake rate of 920 ml used in this study to be closer to the upper percentile of breast milk ingestion (980 ml/day) rather than the mean ingestion rate (688 ml/day), and a child body weight of 7.8 kg was used (average weight for a 2-12 month old, assuming that the mother returned to work full time when the child was 2 months old), and it was assumed that exposure was for 5 days/week, 40 weeks of the year (10 months):

Annual Average Daily Dose=

$$\frac{12.08 \text{ mg/day} \times (688/920 \text{ scaling factor}) \times 5 \text{ days/week} \times 40 \text{ weeks}}{7.8 \text{ kg} \times 365 \text{ days}}$$

This resulted in an annual average dose of 0.63 mg/kg/day.

The sponsor states that the conditions used in this estimate are not expected to occur since many workplaces have a protective reassignment program to minimize potential exposures for pregnant or nursing women. In addition, the sponsor further concludes that even without protective reassignment, continuous workplace exposure to the TLV is not expected to occur. The sponsor's report states that occupational MEK exposure levels reported for U.S. workplaces were all well below the TLV; most values presented in these reviews were <10 ppm (the highest 8 hr TWA occupational exposure level listed in the HSDB was 45 ppm for a study of male workers).

The January 12, 2005, letter from ACC to EPA further clarifies that the sponsors believe that a more realistic upper bound for infant exposure is the Fisher model divided by a factor of 4 (estimated as the TLV divided by the highest reported 8 hr TWA, or $200 / 45 \sim 4$), or 0.16 mg/kg/day (instead of 0.63 mg/kg/day).

Children's Exposure

The sponsor's assessment considered for chronic exposures, naturally-occurring MEK in food was found to be the most significant exposure pathway for children, while higher acute exposures may occur through direct or indirect contact with consumer products brought into the home. The sponsor's exposure assessment was based on an examination of both natural and

anthropogenic sources and of existing measurements of MEK concentrations in various media, including ambient air, soil, and water; food; breast milk; and consumer products. Dietary exposure was assessed by the sponsor by selecting four food items (cheese, yogurt, apple juice, and milk) and estimating intake using available food consumption survey data. A second analysis was done using a wider range of food products. The maximum reported MEK concentration in food for each assessed food category was applied to all foods in the category.

Exposure to MEK in ambient air was evaluated in the sponsor's assessment using available monitoring data. According to the sponsor, existing data for outdoor air indicate a maximum ambient air concentration of 14 ppb, a level which occurred in an urban environment and was not traceable to a point source; indoor air concentrations of MEK ranged from 0.7 to 14 ppb. The sponsor's assessment indicated that data from four available studies of school air quality was limited; MEK was either not detected or it was not stated whether or not MEK was tested. Therefore, potential exposure via indoor air in schools was not quantified in the sponsor's assessment. Furthermore, the sponsor considered the ventilation in school buildings to be better than in residential environments and therefore did not consider MEK concentrations in school buildings to be higher. The possibility that consumer products containing MEK, such as cleaners, polishes, and paints, may be used in greater quantities in schools, and with greater frequency, is not addressed in the sponsor's assessment.

The sponsor's submission briefly discusses the assessment of MEK in water, stating that MEK is generally not detected in surface water, groundwater, and drinking water. Two MEK concentrations in drinking water samples (1.6 ug/L and 4,300 ug/L) were cited in the sponsor's submission. The higher of these figures was of uncertain origin; the water sample may have been taken from any point in the drinking water treatment process. Ignoring that data point, the sponsor's submission reports that exposures based on the lower of the two values would be insignificant based on reasonable expectations for drinking water consumption. Therefore, the sponsor's assessment did not consider water to be a significant exposure route for MEK because of its rapid volatilization and biodegradation in water.

Potential exposure to MEK in soil is discussed very briefly in the sponsor's assessment. The sponsor's submission states that the only available data indicate the presence of MEK in soils only at mines or waste disposal facilities. For this reason, the sponsor's submission concludes that soil is not a likely exposure route for children.

Exposure to MEK from facility emissions is discussed briefly in the sponsor's assessment. A previous EPA study in which a worst-case exposure was calculated is cited. This report outlined the maximum potential exposure, calculated at maximum proximity to the source.

The sponsor's submission presents data pertaining to nursing infant exposure to MEK via the mother's occupational exposure. Using the 95th percentile blood serum concentration and

conservative intake factors from the U.S. EPA Exposure Factors Handbook, the potential exposure to infants via breast milk is 0.0024 mg/kg/day. Using a worst-case scenario, with a high frequency of nursing during the workday, a steady rate of exposure, and a high infant feeding rate, an exposure of 0.63 mg/kg/day was calculated. The sponsor's submission states that actual exposures would be lower than the value calculated. The January 12, 2005, letter from ACC to EPA further clarifies that the sponsors believe that a more realistic upper bound for infant exposure is 0.16 mg/kg/day (instead of 0.63 mg/kg/day).

To assess exposure to MEK through consumer products, the sponsor's submission presents an extensive analysis of products containing MEK. Sources of product data included the Source Ranking Database, the EPA/MRI Household Product Database, and the California Consumer Product Database. Researchers also obtained Materials Safety Data Sheets for many products containing MEK and visited auto supply and hobby stores to examine products containing MEK. Except for hobby model paints and glues, no products containing MEK were found to be marketed specifically to children. Also, within any category of consumer product, not all products and brands contained MEK.

Consumer products were divided into categories in the sponsor's report as follows: automotive cleaners; household cleaners/polishes; paint-related products; fabric and leather treatments; electronic equipment cleaners; oils, grease, and lubricants; adhesives; miscellaneous products; agricultural/pesticide products; personal hygiene items; nail care products; miscellaneous household products; and other construction-related items. Within each category, the product with the greatest weight fraction of MEK was taken to represent weight fractions for the entire category. The automotive products, paint-related products, construction materials, and adhesives categories were evaluated further; other categories were removed from consideration based on a low weight fraction of MEK, a low frequency of appearance of MEK in individual products, or a low likelihood of use by or near children. Justifications for the removal of each category from consideration were provided in the text; in some cases, citations in support of the decision were given.

From the four categories identified for further consideration, the sponsor's submission provides exposure scenarios. The scenarios involve use of a carburetor cleaner, spray paint, wood stain/varnish, paint thinner, modeling cement, and construction materials. For some products, multiple product scenarios are provided. Exposures were modeled using EPA's Exposure and Fate Assessment Screening Tool (E-FAST); some secondary modeling was done using the PROMISE model developed by the American Chemistry Council. Results of the modeling, including rates of exposure for each scenario, are presented in the sponsor's report.

Human Biomonitoring Data

In humans, MEK has been identified as a minor but normal constituent of urine, as a

constituent in the serum and urine of diabetics, and in expired air. Its production in the body has been attributed to isoleucine catabolism. MEK was detected in the blood of more than 75% of the participants of the general population in the Third National Health and Nutrition Examination Survey (NHANES III). Median blood levels were 5.4 ppb. Investigators looked for associations between MEK blood levels and self-reported chemical exposures as collected via the NHANES questionnaire. Blood MEK levels were positively associated with mean daily alcohol intake, and were generally not associated with other environmental exposure variables.

3.0. Summary of Tier 1 Hazard Assessment

Toxicokinetics of MEK

The only available information for absorption of MEK following oral exposures in humans is from case reports of accidental exposures. Data confirming absorption of MEK following inhalation exposures comes from data on industrial workers. Alveolar air concentration of MEK was shown to be highly correlated with the environmental air concentration and averaged 30% of the latter. Pulmonary retention of 70% was estimated for workers exposed to MEK concentrations less than 300 ppm for 4 hours. A physiologically-based model for MEK indicates that steady-state concentrations are reached within 8 hours when exposures are between 50 and 100 ppm. In human volunteers exposed to MEK at 200 ppm for 4 hours, pulmonary uptake ranged from 51 to 55% of the inspired dose. In human volunteers exposed to MEK at 200 ppm for 4 hours, alveolar breath samples reached steady-state concentrations by 2 hours at 5-6% of the exposure concentration. Dermal absorption of MEK in humans is demonstrated by the presence of MEK in the exhaled air within 2.5-3.0 minutes after application to normal skin of the forearm. MEK in exhaled air following dermal exposure reached a plateau in approximately 2 hours.

Data from MEK-exposed industrial workers indicates rapid transfer from the lungs to the blood and distribution throughout the body tissues without accumulation in any particular tissues. In workers, the level of MEK in blood is significantly correlated with environmental air concentration. Postmortem determinations of the MEK tissue/air solubility ratio for human kidney, liver, muscle, lung, heart, fat, and brain revealed similar solubility in all these tissues. The available data suggest that MEK does not accumulate in fatty tissues in humans.

In humans exposed to airborne MEK, 2-butanol and 2,3-butanediol have been identified as MEK metabolites in serum, while 3-hydroxy-2-butanone and 2,3-butanediol have been identified as urinary metabolites. In human volunteers exposed to MEK at 200 ppm for 4 hours, 3% of the absorbed dose was exhaled unchanged as MEK and 2% was excreted in urine as 2,3-butanediol. Since only small amounts of MEK or metabolites were recovered, it is assumed that the majority of the MEK was rapidly metabolized to low molecular weight compounds and incorporated into other molecules.

In humans, MEK is rapidly cleared from the blood with a plasma half-life of 49–96 minutes, exhibiting a biphasic elimination between 30 and 80 minutes. Blood samples collected from 20 volunteers (sex not specified) exposed to 100 or 200 ppm MEK for 4 hours exhibited an elimination half-life of 49 minutes. MEK was not detected in blood at 20 hours post exposure. Given the rapid clearance of MEK, it is unlikely that MEK would accumulate with chronic exposure.

Animal data indicate that MEK is well absorbed following ingestion, inhalation, and dermal exposure. In male Sprague-Dawley rats, a peak plasma concentration following oral exposure of MEK was reached at 4 hours and decreased near baseline 18 hours after exposure. Absorption of MEK following inhalation exposure in rats indicates pulmonary retention of 40% for concentrations less than or equal to 180 ppm for up to 14 hours. Male F344 rats orally administered MEK at a dose of 50 mg/kg had MEK levels in exhaled air peak 1 hour after exposure.

The elimination of MEK and its metabolites in animals occurs rapidly and is essentially complete within 24 hours. MEK is metabolized in the liver via hydroxylation to 3-hydroxy-2-butanone which is subsequently reduced to 2,3-butanediol. A minor metabolite is 2-butanol which is rapidly oxidized back to MEK. MEK and its metabolites are primarily excreted via the lungs with small amounts excreted via the kidneys. The hydroxylated metabolites are eliminated in the urine as o-sulfate or o-glucuronide conjugates or enter the intermediary metabolism to be eliminated as CO₂ or incorporated into tissues.

The pharmacokinetics and metabolism of MEK and 2-butanol in animals are interrelated and animal toxicology data indicate that each is a good surrogate for the other. 2-butanol is rapidly absorbed and primarily metabolized to MEK. The toxicities of MEK and 2-butanol in animals is very similar, and it is assumed that the metabolic relationship between MEK and 2-butanol in humans is similar to that in rats. In experimental animals, 2-butanol is rapidly metabolized to MEK as shown by blood levels of MEK following oral exposure. Both MEK and 2-butanol further generate similar levels of the metabolites 3-hydroxy-2-butanone and 2,3-butanediol.

There was no significant difference in area under the curve (AUC) of MEK blood concentration after oral dosing of rats with either 1776 mg/kg 2-butanol or 1690 mg/kg MEK (10,899±842 or 9,868±566 mg-hour/liter respectively). Approximately 97% of 2-butanol was converted to MEK. Peak blood concentrations of MEK and metabolites were similar whether MEK or 2-butanol were administered, with a shift of approximately 4 hours to reach peak concentrations when 2-butanol was administered.

Toxicity Data in Humans

Human data available on MEK include cancer and neurotoxicity studies and include case reports, reports on volunteers, and occupational studies.

In a series of studies conducted on volunteers by NIOSH, no statistically significant increase in symptoms of throat irritation were reported by investigators, nor did they find marked performance changes in a series of tests of psychomotor abilities, postural sway, and moods in subjects exposed to 200 ppm MEK for 4-hours. Another study assessed potential irritation of MEK to mucous membranes in 19 volunteers after a 4-hour exposure to 200 ppm. No statistically significant adverse effects were reported via questionnaire. Earlier studies (exposures in industrial settings prior to 1950) reported slight nose and throat irritation after exposure to 100 ppm and mild eye irritation at 200 ppm after 3-5 minutes exposure. However, this study as well as another study which reported headache and throat irritation at 300 ppm and nausea and vomiting at 500 ppm for an unspecified duration of exposure are limited by inadequate exposure information. Several occupational studies examining the effects of chronic exposure to MEK have been conducted; however, they are limited by co-exposures to other solvents, lack of adequate exposure information, and study design problems.

Retrospective mortality studies assessing the carcinogenic effects of chronic MEK exposure have not indicated any excess in cancer deaths in industrial workers; however, some evidence suggests an increased risk between multiple solvent exposure, which included MEK as a component, and certain cancers among workers in a degreasing plant. Because of various study limitations (including small sample size, small numbers of cases, and multiple solvent exposures), these studies are not adequate to support conclusions about the carcinogenic potential of MEK in humans.

Toxicity Data in Animals

Mutagenicity

MEK was negative in a reverse mutation assay in *Salmonella typhimurium* and in an assay in *Escherichia coli*, and it did not cause mitotic gene conversion in the yeast, *Saccharomyces cerevisiae*. The tests in *S. typhimurium* and *E. coli* were conducted with and without metabolic activation. MEK did not induce mutation in mouse lymphoma L5178Y TK⁺ cells in culture nor did it cause cellular transformation in the BALB 3T3 assay. MEK did not induce chromosomal aberrations or sister chromatid exchanges in rat liver cells in vitro or unscheduled DNA synthesis in rat primary hepatocytes. MEK also did not induce micronuclei in the bone marrow of mice or hamsters after i.p. injection.

MEK did induce chromosomal malsegregation in a study of aneuploidy in *S. cerevisiae*.

but did not induce mitotic recombination or point mutation. Low levels of MEK combined with low levels of nocodazole which is an inducer of aneuploidy have also produced aneuploidy in the *S. cerevisiae* test system.

Acute Toxicity

The potential acute toxicity of MEK has been studied in multiple animal species (rats, rabbits, mice, and guinea pigs) via multiple routes of administration (oral, inhalation, dermal). Lethality and sensory irritation have been the primary focus in these studies. Overall, the available data indicate MEK has low acute toxicity. Oral LD₅₀ of MEK in rats and mice is reported to be between 2 and 5 g/kg. A single gavage dose of approximately 1 g/kg in corn oil produced no deaths or histological alterations in the livers of male rats, but did produce tubular necrosis in the kidneys. Acute inhalation 4-hour LC₅₀ in guinea pigs was between 10,000 and 33,000 ppm. In mice, a 45-minute LC₅₀ of 69,400 ppm and a 4-hour, 14-day LC₅₀ of 12,000 ppm have been reported. In rats, the two-hour LC₅₀ was estimated to be between 2,000 and 4,000 ppm. Results from multiple studies in rats indicate the best estimate of the 4-hour LC₅₀ may exceed 5,000 ppm, and may even exceed 10,000 ppm. The rabbit dermal LD₅₀ of MEK has been reported at greater than 5 g/kg and greater than 13 g/kg.

In inhalation studies of mice, the concentration to elicit 50% decrease in response rate to visual stimuli, or EC₅₀, was 2,891 ppm. A similar EC₅₀ of 2,065 ppm for behavioral effects was reported for mice exposed to MEK for 4-hours and then subjected to the behavioral despair swimming test.

MEK was not a contact allergen in the mouse ear-swelling test and there was no evidence of MEK-induced skin sensitization of albino guinea pigs in a study where MEK was used as the vehicle control/solvent. MEK has been rated as a 2 out of a possible 10 for dermal irritancy to albino rabbits. In an interlaboratory comparison of the skin irritancy of solvents to albino rats, MEK was rated as a skin irritant by 12/22 laboratories with irritancy values ranging from 0 to 3.2 out of a possible 30.

No sensitization reactions were seen in human volunteers exposed to a mixture of 20% MEK in petroleum jelly and no irritation was seen following a 48-hour closed-patch test in humans.

Repeated Dose Toxicity Following Oral Exposure

There is no chronic bioassay of MEK via oral exposure. In addition, there are no studies examining the subchronic effects of oral exposure to MEK in experimental animals. The repeat-dose oral toxicity data base is limited to data for 2-butanol, a metabolic precursor, and 3-hydroxy-2-butanone, a metabolite.

Data from the 13-week drinking water study with 3-hydroxy-2-butanone in CFE rats suggest a possible adverse hematological effect (slight anemia, as indicated by decreased hemoglobin concentration and red blood cell count). This effect, however, is not consistent with the hematological findings in studies of 2-butanol (oral and inhalation exposure) or MEK (inhalation exposure). Thus, 3-hydroxy-2-butanone does not appear to be an appropriate surrogate for assessing the oral toxicity of MEK.

Repeated Dose Toxicity Following Inhalation Exposure

There is no chronic bioassay of MEK via inhalation exposure. While a high quality subchronic inhalation toxicity study in rats is available, it is of questionable value for quantitative risk assessment due to the potential effect of a suspected infectious agent confounding the ability of the study to address portal-of-entry effects in the respiratory tract. In this study, male and female Fischer 344 rats (15/sex/group) were exposed in a whole body dynamic air flow chamber to MEK 6 hours/day, 5 days/week for 90 days. The reported time-weighted average exposure concentrations of MEK were 0, 1,254, 2,518, or 5,041 ppm (0, 3,700, 7,430, or 14,870 mg/m³). At the study termination, 10 animals/sex/group were subject to routine gross pathology and histopathology. Special neurohistopathological studies were conducted on the medulla and the sciatic and tibial nerves of the remaining five male and female rats from each group.

Reported effects remote to the respiratory tract in the 5,041 ppm animals are of uncertain biological significance. These effects include: reduced body weight gain, statistically significant increases in relative liver weight (males and females) and altered serum liver enzymes (females), and decreased brain weight (females). The authors judge that liver effects are more likely indicative of a physiological adaptive response than toxicity. The finding of decreased brain weight observed in female rats raises concerns, but is difficult to interpret. Generally, with a brain weight reduction of 5%, one might expect evidence of corresponding pathology; however, no treatment-related brain pathology was observed in this study. The reduction in brain weight relative to controls observed in only one sex also raises questions about the relevance of the finding. Thus, while the reduction in brain weight at 5,041 ppm is noteworthy, its biological significance is uncertain.

Numerous repeat-dose studies focus on neurological endpoints. Animal studies provide no convincing evidence that exposure to MEK alone causes nerve degeneration or other persistent neurotoxic effects. A study found no evidence of peripheral neuropathy (as indicated by paralysis) following continuous exposure of 12 Sprague-Dawley rats to 1,125 ppm (3,318 mg/m³) MEK for 16 to 55 days. Another study found no neurological effects in special neuropathological studies of the medulla and sciatic and tibial nerves of rats exposed to MEK at concentrations up to 5,041 ppm (14,870 mg/m³) for 90 days. Male Wistar rats (8 per group) exposed to 200 ppm (590 mg/m³) MEK 12 hours/day for 24 weeks show no evidence of a persistent effect on motor or mixed nerve conduction velocity, distal motor nerve latency, or

histopathological lesions of tail nerves. An early experiment exposed 4 cats, 4 rats, 5 mice, and an unknown number of chickens to 1,500 ppm (4,425 mg/m³) MEK 24 hours/day, 7 days/week for 7-9 weeks with no apparent adverse neurologic effects.

Cancer

No chronic/carcinogenicity studies exist for MEK by any route of exposure.

Reproductive Toxicity

No studies were located that specifically assessed the reproductive toxicity of either inhaled MEK or 2-butanol, a metabolic precursor, or of the MEK metabolites, 3-hydroxy-2-butanone and 2,3-butanediol. Although no tests for reproductive function were performed, histological examination of the reproductive organs from rats of both sexes and mammary glands of female rats exposed subchronically to MEK at concentrations as high as 5,000 ppm (14,750 mg/m³) revealed no exposure-related lesions.

No studies concerning reproductive toxicity of MEK exposure by the oral route are available. No oral repeat-exposure animal studies or human exposure data were located for 2,3-butanediol. A 13-week drinking water study with 3-hydroxy-2-butanone is available. No effects on reproductive organs were reported. A multigeneration reproductive toxicity study of 2-butanol via the oral route is available and summarized below. Although the study was adequately-conducted and the critical effect demonstrated therein was supported by inhalation studies with MEK, a metabolic surrogate was used in place of MEK and the highest drinking water concentration was reduced during the study resulting in a need to estimate the actual exposure dose. Furthermore, certain parameters routinely evaluated in studies of more current design (e.g., estrous cyclicity, sperm parameters, and uterine weight) were not measured.

Weanling FDRL-Wistar stock rats (30/sex/group) were given 2-butanol in drinking water at 0, 0.3, 1, or 3% solutions and a standard laboratory ration *ad libitum*. Exposure to 3% 2-butanol in drinking water for 8 weeks caused reduced weight gain in adult F0 males and females. Because increased mortality and decreased body weight occurred in the F1A litters at the 3% dose level, all high-dose parents and F1A offspring were given drinking water without 2-butanol between days 10 and 21 of lactation and then 2% 2-butanol for the remainder of the experimental protocol. F1 animals exposed to 2-butanol in drinking water at concentrations up to 2% for 12 weeks after birth and through mating, gestation, and lactation of F2 litters were subject to gross and histopathological examination. No exposure-related changes in organ weights or incidence of histopathologic lesions were observed with the exception of specific histopathologic changes of the kidney in male rats exposed to 2% 2-butanol. Changes were consistent with the pattern of early stages of α_{2u} -globulin-associated rat nephrotoxicity; however, testing needed to demonstrate the presence of α_{2u} was not conducted. Therefore, the relevance of this finding to humans is

uncertain. The administration of 2-butanol in drinking water before and during gestation and lactation at concentrations as high as 3% did not affect reproductive performance, with the possible exception of increased male copulatory failure. The incidence of male F0 rats that did not successfully copulate with F0 females was: 0% (1/30), 0.3% (2/30), 1% (0/30), and 3% (6/30). Data from which to determine copulatory failure were not provided for other generations. In addition, reduced body weight gain in this high-dose group could have contributed to copulatory success. For these reasons, the biological significance of these data for the F0 generation males is uncertain.

Developmental Toxicity

Several well-conducted inhalation developmental toxicity studies on MEK are available in rats and mice. Three inhalation developmental studies in rodents demonstrated that MEK caused developmental toxicity in the presence of maternal toxicity in rats and mice, and in one rat study, in the absence of maternal toxicity. These inhalation studies provide evidence for developmental effects (decreased fetal weight and increased incidence of certain skeletal variants) in rats and mice exposed to 3,000 ppm MEK, 7 hours/day during gestation, but not at 1,000 ppm and lower. The observation of developmental delays following inhalation exposure to MEK is supported by the findings from studies of rats exposed orally and by inhalation to 2-butanol, a metabolic precursor of MEK.

Additional information relevant to the developmental toxicity of inhaled MEK is provided by a developmental inhalation toxicity study of exposed gravid Sprague-Dawley rats by inhalation to 2-butanol at 0, 3,500, 5,000, or 7,000 ppm (0, 10,605, 15,150, or 21,210 mg/m³) for 7 hours/day on gestation days 1-19. Maternal toxicity was exhibited in the dams at all three exposure concentrations as statistically significant reductions in weight gain and food consumption. The authors reported narcosis (impairment of locomotor activity) at 5,000 ppm and above. Effects on certain fetal developmental indices were also reported. A statistically significant increase in the incidence of pooled skeletal variations was observed at 7,000 ppm (100%) when compared to controls (32%). The authors did not report the nature of skeletal variations observed or the incidence of individual variations. Occasional visceral variations were seen; however, the authors did not attribute these to 2-butanol treatment. External fetal malformations were not observed. A statistically significant increase in the number of resorptions per litter was reported at 7,000 ppm (3.8±2.2) compared with the control (1.5±1.3). Fetal weights were reduced in all 2-butanol-exposed groups; differences were statistically significant when compared to the control at 5,000 and 7,000 ppm.

No studies concerning the developmental toxicity of MEK exposure by the oral route are available. A study is available, however, of the reproductive and developmental toxicity of 2-butanol, a metabolic precursor of MEK. As described above, data from rats suggest that almost all (96%) of an administered dose of 2-butanol is converted to MEK, and that both chemicals are

metabolized through the same intermediates. Thus, developmental toxicity data from oral exposure to 2-butanol are considered relevant to MEK

The oral toxicity data base for 2-butanol consists of a combined two-generation reproductive toxicity and prenatal developmental toxicity study in Wistar rats. Decreases in pup survival and pup body weight gain were observed. A concentration of 2% in drinking water caused a reduction in fetal weights when pregnancies were terminated on gestation day 20 and decreased pup body weights when dams were allowed to deliver. A LOAEL of 3,122 mg/kg-day (2% solution) and a NOAEL of 1,771 mg/kg-day (1% solution) for decreased fetal weight and decreased pup body weight gain were reported. The findings of developmental toxicity in rats exposed orally to 2-butanol is consistent with similar findings in inhalation developmental toxicity studies of MEK. Given these observations, it is plausible that the developmental effects produced by 2-butanol and MEK are caused by MEK or a subsequent metabolite common to both.

No information concerning the potential for developmental effects from exposure to 3-hydroxy-2-butanone (a metabolite) exists. This observation further supports the use of 2-butanol (a metabolic precursor), rather than a metabolite, as a surrogate for MEK.

Developmental Neurotoxicity

No specific, guideline quality developmental neurotoxicity studies via any route of exposure have been conducted on MEK or on 2-butanol. A few animal studies involving a single or limited number of inhalation exposures reported behavioral effects and narcosis. However, several well-conducted repeat-dose toxicity studies in experimental animals examined for both neurological function and for central nervous system lesions using special neuropathological procedures provide no convincing evidence that repeated exposure to MEK, by itself, is capable of producing persistent neurological effects. No persistent, treatment-related central or peripheral neural histopathology was observed in rats exposed by inhalation for 90 days (6 hours/day, 5 days/week) to MEK at concentrations up to 5,041 ppm (14,870 mg/m³). Repeated inhalation exposure of rats and mice to MEK at approximately 3,000 ppm (8,850 mg/m³) (7 hours/day during days 6–15 of gestation) produced no overt neurological effects in the dams. The potential exists, however, for increased susceptibility to neurotoxicity following exposure to MEK in combination with certain other solvents. MEK, for example, potentiates the neurotoxicity of hexacarbon solvents (n-hexane, MnBK, and 2,5-hexanedione).

Immunotoxicity

Studies designed to specifically examine the potential for immunotoxicity for MEK by any route of exposure were not available. The only evidence suggestive of possible immune system effects were reported in a 90-day repeat-dose inhalation toxicity study in rats in which a

statistically significant 5% decrease in absolute spleen weight (without any corresponding histopathology) was observed in high-dose (5,041 ppm) females. No other immune system effects were reported in any other studies. Furthermore, MEK was not a contact allergen in the mouse ear-swelling test, there was no evidence of MEK-induced skin sensitization, and MEK produced no sensitization reactions or irritation in human volunteers.

4.0 Summary of Tier 1 Risk Characterization

The sponsor's risk characterization combined the information in the Hazard Assessment and Exposure Assessment to assess the potential risks to children from reasonably anticipated exposures to MEK. The sponsor's risk assessment focused primarily on potential exposures to children from man-made sources that included ambient exposures (air, water, soil, and facility releases), indoor air, breast milk from occupationally exposed mother, and consumer products. Potential aggregate chronic exposures for the selected consumer product use scenarios were also evaluated.

The only MEK exposure pathway assessed by the sponsors unique to children was breast milk. The sponsor's exposure assessment did not include a thorough evaluation of prospective parents or pregnant women as a target population. Values for daily aggregate exposures were not provided. The potential for transfer of MEK to a child from parental skin or clothing was not considered in the assessment because the sponsor deemed these potential exposures to be minimal since the relatively high vapor pressure and ready evaporation of MEK would dissipate before contact at home could occur.

For exposures to ambient and indoor air levels of MEK, the sponsor's assessment finds no risk to children. MEK has been detected in ambient and indoor air at very low levels, in the range of a few parts per billion; these levels are far below the IRIS RfC of 5.0 mg/m³ (based on misaligned sternalbrae in mice exposed to MEK by inhalation).

For exposures to sources of drinking water (surface or groundwater), the sponsor's report also asserts no risk to children. A single confirmed sample of drinking water was found to contain 1.6 ppb. The sponsor concluded that if all sources of water were to contain MEK at that concentration, the estimated daily consumption of MEK in water for a child who consumes one liter of water per day would be 1.6 µg, orders of magnitude below the IRIS RfD of 0.6 mg/kg/day (based on decreased fetal birth weight in rats exposed to 2-butanol in drinking water).

Since the potential for children's exposure to MEK in the soil appears to be minimal, the risk was also considered by the sponsor to be minimal; a literature search conducted by the sponsor did not identify any measurements of MEK in soil and, according to the sponsor, the physical/chemical properties of MEK make it unlikely to persist in soil.

For environmental releases of MEK from industrial facilities, the sponsor concludes that

facility releases are not expected to pose any health risks. According to the sponsor's report, releases to soil and water are minor and are not expected to result in significant exposures. The sponsor has pointed out that EPA has granted the petition to delete MEK from the list of hazardous air pollutants (HAPs). EPA's assessment in response to the petition to delist MEK from HAPs concluded that maximum modeled annual average air concentrations are expected to be well below the RfC, with actual human exposures expected to be much lower; therefore, releases to air are also not expected to result in adverse health effects.

The sponsor also considered potential exposures of children to MEK in breast milk of an occupationally exposed mother. They took into account what they characterized as several conservative assumptions and concluded that upper bound estimates of this potential source of exposure were either at or below the RfD. The sponsor further concluded that actual exposures to children via breast milk are likely well below levels that might pose health risks.

The sponsor estimated children's potential chronic exposures to MEK for several categories from selected consumer product use scenarios (from paints to food uses) for six age groups using assumptions intended to overestimate exposure (Table 1, taken from Table 9.1 from the sponsor's assessment). Depending on the age group (< 1 year - 19 years of age), children were assumed to have either direct exposure from use of the product; or passive, secondary exposure through adult uses of products. Exposures were estimated for the day of use and for repeated, chronic use over time. Conservative estimates of potential chronic exposures were expressed in mg/kg/day and compared to the IRIS RfD of 0.6 mg/kg/day. Chronic estimates were based upon a 90th percent use frequency occurring each and every year, and assumed all product use to be indoors and MEK to be present in all products used. In every case, potential chronic exposures were well below the RfD for all age groups. Margins of Safety (MOS) for chronic exposures were determined by dividing the IRIS RfD of 0.6 mg/kg/day by the estimated exposure for each age group. Since lifetime exposure at the RfD is deemed to be without appreciable health risks, any MOS greater than 1 were considered by the sponsor to be indicative of no likely health risk. MOSs ranged from 37.5-30,000. The sponsor concluded that repeated use of these products over time should not be expected to pose significant health risks to children in any age group.

**Table 1 Children's Potential Chronic Exposures to MEK
from Selected Consumer Product Use Scenarios**

Use Scenario	Exposure by Age Group (mg/kg/day)	Exposure by Age Group (mg/kg/day)						Margin of Safety
		<1 yr	1-2 yrs	3-5 yrs	6-11 yrs	12-15 yrs.	16-19 yrs	
Carburetor Cleaner	Passive	0.0003	0.0003	0.0002	0.0002	0.0001	0.0001	2,000 to 6,000
	Active						0.0003	2000
Spray Paint	Passive	0.008	0.007	0.006	0.005	0.003	0.003	75 to 200
	Active						0.008	75
Wood Stains/Varnishes	Passive	0.016	0.014	0.012	0.010	0.006	0.005	37.5 to 120
	Active						0.016	37.5
Paint Thinner								
Scenario 1: Addition to liquid wood stain/varnish before painting								
	Passive	5.9E-05	5.3E-05	4.5E-05	3.6E-05	2.3E-05	2.0E-05	10,169 to 30,000
	Active						7.0E-05	3,571
Scenario 2: Brush cleaning								
	Passive	0.0013	0.0011	0.0010	0.0008	0.0005	0.0004	462 to 1500
	Active						0.008	75
Scenario 3: Use in Dermal Clean Up								
	Active only						0.0013	462
Adhesives								
Scenario 1: Dermal Exposure during hobby use								
	Active					0.00007	0.00007	3,571
Scenario 2: Inhalation during hobby glue use								
	Not in Room	0.0004	0.0003	0.0003	0.0002			1,500 to 3,000
	In Room					0.0004	0.0004	1,500
Scenario 3: Inhalation during adult use								
	Not in Room	0.0001	0.0001	0.0001	0.00009	0.00006	0.00005	5,000 to 12,000
	In Room	0.0004	0.0004	0.0003	0.0003	0.0002	0.0001	1,500 to 6,000
Hobby Model Painting								
	Not in Room	0.0006	0.0005	0.0004	0.0003			1,000 to 2,000
	In Room					0.0006	0.0005	1,000 to 1,200

Children's potential acute exposures were also estimated for the same selected consumer product use scenarios as with chronic exposures (Table 2, taken from table 9.2 from the sponsor's assessment). The sponsor states that acute exposures can result in higher acute daily doses but that as MEK is rapidly metabolized, acute exposures do not lead to increased body burden over time. Margins of exposure (MOEs) for acute exposures were determined by dividing the NOAEL (200 ppm or 590 mg/m³) for sensory irritation by the estimated 4-hour TWA exposure for each scenario. All MOEs for acute exposures were greater than 1, ranging from 6-20,000. Four-hour TWAs were significantly below the NOAEL of 200 ppm indicating low concern for potential acute effects from use of these products.

The sponsor also considered the potential for annualized aggregate chronic exposures for the selected consumer product use scenarios from representative consumer products thought to represent the highest potential for exposure for all age groups. The sponsor's assessment states that analysis of consumer products indicates that MEK is typically present in only a fraction of available brands for a given type of product. The sponsor used what they characterize as conservative assumptions; chronic exposure values were estimated on the assumptions that MEK was present in 100% of the brands for each product, that there was a 90th percentile use frequency for each and every year, and that all products were intended for use by children. The sponsor's assessment concluded that these exposures are in most cases, well below the RfD or RfC and that there did not appear to be a reasonable basis for concern that multiple sources of MEK exposures might in the aggregate pose significant health risks to children.

**Table 2 Children's Potential Acute Exposures to MEK
from Selected Consumer Product Use Scenarios**

Use Scenario		4 hr TWA- mg/m ³	Margin of Exposure
Carburetor Cleaner			
Maximum Use	Passive	1.2	492
	Active	3.9	151
Median Use:	Passive	0.3	1967
	Active	1.0	590
Spray Paint			
Maximum Use	Passive	19.9	30
	Active	56.00	11
Median Use:	Passive	9.4	53
	Active	26.6	22
Wood Stains/Varnishes			
Maximum Use	Passive	30	20
	Active	92	6
Median Use	Passive	19	31
	Active	57	10
Paint Thinner			
Scenario 1: Addition to liquid wood stain/varnish before painting			
Maximum Use	Passive	0.5	1180
	Active	1.9	311
Median Use	Passive	0.03	19666
	Active	0.12	4917
Scenario 2: Brush cleaning			
Maximum Use	Passive	0.7	343
	Active	13.7	43
Adhesives			
Scenario 1: Inhalation during hobby glue use			
Maximum Use Hobby model glue at 40% MEK	Not in Room	0.15	3933
	In Room	0.43	1372
Alternate Maximum Use 100% MEK, 0.07 oz used	Not in Room	0.05	11800
	In Room	0.15	3933

**Table 2 Cont'd Children's Potential Acute Exposures to MEK
from Selected Consumer Product Use Scenarios**

Use Scenario		4 hr TWA- mg/m ³	Margin of Exposure
Scenario 2: Inhalation during adult use			
Maximum Use	Not In Room	1.0	590
	In Room	3.2	184
Median Use	Not In Room	0.07	8429
	In Room	0.2	2950
Hobby Model Painting			
Maximum Use	Not In Room	0.14	4214
	In Room	0.4	1475
Median Use	Not In Room	0.07	8429
	In Room	0.20	2950

5.0. Summary of the Sponsor's Tier 2 Data Needs

The sponsor considers the exposure assessment as having used conservative assumptions such that the margins of safety are more likely to be understated rather than overstated. The sponsor believes the information presented in the assessment demonstrates that reasonably anticipated exposures to MEK are not likely to exceed relevant health benchmarks and are not likely to present significant health risks to children. While the sponsor acknowledged there are data gaps in the existing exposure data, these data gaps are not identified as data needs by the sponsor and any additional exposure assessment work is considered a low priority.

The sponsor has identified data gaps for Tiers 2 and 3. Tier 2 data gaps include the lack of an immunotoxicity study. Tier 3 data gaps include the lack of a chronic/cancer bioassay and a developmental neurotoxicity study. The sponsor does not consider the existing data base on MEK or its metabolic precursor, 2-butanol, as being suggestive of or having the potential to cause immune system, developmental neurotoxic, or carcinogenic effects and considers the weight of evidence from existing studies on MEK demonstrates low acute and systemic toxicity. Therefore, the sponsor does not characterize any of these data gaps as data needs and sees no justification for conducting additional toxicity studies.

6.0. EPA Response to the Sponsor's Tier 2 Data Needs

EPA agrees with the approach of using quantitative estimates of risk to help inform decisions about the potential impact of additional exposure or toxicity studies, and therefore assist in determining whether "data gaps" are actually "data needs". As discussed above, the sponsor used a qualitative estimate of exposure with several different receptor populations and an IRIS RfD and RfC to quantitate the hazard potential of MEK. EPA agrees that these are useful exposure approaches for assessing potential risks to children (or prospective parents) from exposure to MEK.

EPA generally agrees with the sponsor's approach in the exposure assessment and agrees that all tier 1 exposure analyses have been conducted. EPA does not recommend any tier 2 exposure studies for VCCEP.

EPA has reviewed the toxicology data base for MEK and agrees that all Tier 1 studies have been conducted. EPA also notes that several toxicity studies in Tier 2 have been conducted. An oral multigenerational reproductive toxicity study of 2-butanol is available; EPA considers this an adequate surrogate for assessing the potential reproductive toxicity for MEK. There appear to be adequate prenatal developmental toxicity studies with both MEK and 2-butanol in two species, rats and mice. A Tier 2 data gap is the immunotoxicity study; however available data from the numerous repeat-dose and acute toxicity studies do not indicate the immune system as a target for toxicity, therefore, EPA does not perceive an immunotoxicity study as a data need at this time.

Tier 3 data gaps include the chronic toxicity/carcinogenicity, the neurotoxicity screening battery, and developmental neurotoxicity study. However, none of these Tier 3 data gaps are perceived by EPA as data needs at this time. Numerous repeat-dose toxicity studies in adult animals focusing on neurological endpoints did not provide any convincing evidence that exposure to MEK alone causes nerve degeneration or other persistent neurological effects. Likewise, there is no evidence from any of the repeat-dose studies in adult animals or in any of the developmental/reproductive toxicity studies to support a concern for developmental neurotoxicity. And finally, given the negative mutagenicity studies, rapid clearance of MEK, and the unlikely possibility that MEK would accumulate with chronic exposure, there is no basis to support a concern for any chronic or carcinogenic effects.