



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Andrew M. Jaques, Director
Benzene, Toluene, and Xylene (BTX) VCCEP Consortium
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Jaques:

Thank you for coordinating Benzene, Toluene, and Xylenes VCCEP Consortium's sponsorship and assessment activities regarding benzene in EPA's Voluntary Children's Chemical Evaluation Program (VCCEP). EPA truly appreciates the contributions of the Consortium and its member companies (BP Amoco Chemical Company, Chevron Phillips Chemical LP, E.I. du Pont de Nemours & Company, ExxonMobil Chemical Company, Equistar Chemicals LP, Flint Hills Resources LP, Marathon Petroleum LLC, Shell Chemical LP, Sterling Chemical Company, Sunoco Inc., and TOTAL Petrochemicals U.S.A.) to VCCEP.

The purpose of this letter is to inform the Consortium and its member companies of EPA's VCCEP Tier 2 Data Needs Decision for benzene. In formulating this decision, EPA has considered all available information, including the assessment provided by the Consortium and the report of the VCCEP Peer Consultation Panel that provided comments on the Consortium's assessment for benzene. EPA has determined that additional data beyond the assessment prepared by the Consortium are needed to adequately characterize the risks of benzene to children.

EPA has determined that the Tier 1 exposure assessment is not complete. Manufacturing, use, and processing emissions data, monitoring data, outdoor air exposure scenarios, and environmental fate have not been adequately addressed. In addition, there are many transparency issues. Additional details regarding EPA's exposure data needs are provided in the Enclosure.

EPA has determined that all VCCEP Tier 1 toxicity studies have been conducted, as well as several Tier 2 toxicity studies. Although no Tier 2 toxicity data needs have been identified by EPA at this time for VCCEP, EPA has identified two data needs for Tier 3 toxicity studies: a developmental neurotoxicity (DNT) study and an adult neurotoxicity screening battery.

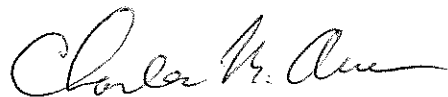
In addition, I am sure you are aware that the Agency for Toxic Substances and Disease Registry (ATSDR) has identified Priority Data Needs (PDNs) for benzene that include: (1) an intermediate duration toxicity study (i.e., 15-364 days) via oral exposure that includes extended reproductive organ histopathology and (2) a pre-natal developmental toxicity study via oral exposure (Federal Register; December 13, 2005; 70 FR 73749). EPA believes that it may be possible to conduct the two Tier 3 toxicity studies identified as data needs for VCCEP via the oral route in a manner that enables ATSDR's PDNs to also be met. Specifically, the adult neurotoxicity screening battery would need to be modified to include extended reproductive organ histopathology, and the DNT study may meet the need for the prenatal developmental toxicity study or, if necessary, it could be modified to include some additional endpoints. I have discussed this approach with ATSDR and believe this approach is the most efficient path forward for the VCCEP sponsors of benzene and the two Agencies. Additional details regarding EPA's toxicity data needs are provided in the Enclosure.

EPA's Data Needs Decision document will be posted to the VCCEP website, along with this decision letter, so that other stakeholders are informed of the status of this review.

Because there are no Tier 2 toxicity data needs identified by EPA at this time for VCCEP, we encourage the Consortium and its member companies to commit to sponsor benzene in Tier 3 of VCCEP which would involve conducting the two needed toxicity studies and submitting revised hazard, exposure, and risk assessments. If the Consortium sponsors benzene in Tier 3, then the deficiencies identified by EPA in the Tier 1 exposure assessment can be addressed by the Consortium in the revised exposure assessment provided as part of the Tier 3 submission. The design of VCCEP specifies that sponsor companies make commitments to Tier 2 or Tier 3 within four months of receiving EPA's Data Needs Decision. (*See* 65 FR 81700, December 26, 2000).

We look forward to hearing from you on this issue. Please contact Jim Willis, the 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. Jim can be reached at (202) 564-4760.

Sincerely,



Charles M. Auer
Director, Office of Pollution Prevention
and Toxics

Enclosure

VOLUNTARY CHILDRENS CHEMICAL
EVALUATION PROGRAM:
DATA NEEDS ASSESSMENT
OF BENZENE

Prepared By
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Office of Pollution Prevention & Toxics
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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/chemrtk>.

In March 2006, the American Chemistry Council's Benzene, Toluene, and Xylenes VCCEP Consortium (ACC) submitted its Tier 1 assessment of Benzene 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 also reviewed a report of a peer consultation panel that provided comments on the assessment; this report is available at www.tera.org.

1.0 Summary of EPA Recommendations

1. At this time, the Tier 1 exposure assessment is not complete. Manufacturing, use, and processing emissions data, monitoring data, outdoor air exposure scenarios, and environmental fate have not been adequately addressed. In addition, there are many transparency issues.
2. All Tier 1 toxicity studies have been conducted under VCCEP, as well as several Tier 2 toxicity studies. No Tier 2 toxicity data needs have been identified. The neurotoxicity screening battery in adults and a developmental neurotoxicity study have been identified as Tier 3 data needs.

2.0 Summary of the Sponsor's Exposure Assessment

Production, Applications and Fate

The sponsor's assessment states that approximately 2 – 3 billion gallons of 'isolated or pure benzene' is produced annually, and is consumed as a chemical feedstock for the production of cumene, ethylbenzene, and other chemical intermediates. Benzene is also a constituent of fuels, with unleaded gasoline typically having a benzene content of 1%. Sponsor's assessment also states that benzene is not used in consumer products.

The sponsor's assessment notes that benzene exposure sources have been regulated for many years, and also states that mobile sources are a large portion of ambient sources of benzene.

The assessment provides a broad overview of the total production. The assessment states that "Pure benzene is isolated", with the petroleum industry being the primary producer. The assessment also contains a breakdown (Table 5.4) of benzene production from the three primary processes, inputs and percentages generated stated as catalytic reforming (straight run gasoline) at 45%, catalytic dealkylation (toluene or toluene/Xylene mixture) at 30%, and steam cracking (pyrolysis gasoline) at 23%. (Agency for Toxic Substances and Disease Registry (ATSDR), 2005)

Historical benzene production levels and production capacity by petroleum producers are culled from trade publications, with most of the benzene production capacity being found

in Texas. Table 5.9 in the sponsor's submission cites a variety of processes in which benzene is released to air. These processes include benzene production processes (such as those previously mentioned above) as well as several other processes not related to the direct manufacture of benzene, such as the combustion of fuel.

The sponsor's assessment provides minimal data on releases to soil and water, primarily confined from leaks of gasoline that contains benzene.

The assessment also includes discussion of the decrease in the national emissions of benzene, which is mainly attributed to the Clean Air Act of 1970. Submission also cites significant decreases at the state level, with a 79% reduction from 1989 to 2001 in the state of California and the Houston-Galveston, Texas area. However, this reduction is mainly attributed to mobile vs. stationary sources, as stated in the submission: "This drop in ambient benzene concentrations is largely a result of the decrease in mobile source emissions due to fleet turnover, Tier 1 car emission standards, and use of reformulated gasoline."

Environmental Fate Properties

The sponsor's fate assessment consisted of a summary paragraph and Table 5.3 which provided some qualitative (e.g., high, moderate, high) environmental fate and transport characteristics for benzene. The summary paragraph extrapolated from the qualitative table indicates that benzene would partition to air, have limited partitioning to water, is relatively mobile in groundwater, biodegrades when a sufficient amount of dissolved oxygen is available, would not bioconcentrate appreciably in marine organisms or plants, and degrades rapidly due to reaction with atmospheric hydroxyl radicals.

Personal Exposure

The contribution from "Chain-of-Commerce" sources and releases are prefaced for both occupational and children's exposure to benzene, and uses the EPA Total Exposure Assessment Methodology (TEAM) Studies, which took place between the 1980's and 1990's, as the primary reference. The sponsor emphasized three conclusions from this study: indoor benzene exposures were greater than outdoor exposures; there was 'no effect on personal exposure of living close to major fixed sources of benzene (oil refineries, storage tanks, chemical plants, etc.)' *in the six cities studied*; and most benzene exposure is caused by personal activities such as cigarette smoking or riding in an automobile.

Occupational Exposure

Occupational exposure to benzene was cited to occur in the two occupation types of production / processing of benzene and use of benzene as a feedstock. There was no information given on neither the number of overall workers in these occupations, nor the number of workers for each of the three primary processes, which produce benzene (listed above).

Members of the sponsors' consortium (ACC BTX) provided data for the broad categories of manufacturing and distribution, representative for employees who are *not* required to wear respirators. Manufacturing operations showed a mean of 0.11 ppm and 95th percentile of 0.39 ppm from 6,443 samples and distribution operations showed a mean of 0.07 ppm and 95th percentile of 0.06 ppm out of 42 samples. No additional information was given as to the activities involved with or processes exposed to in the sampling pool, including those workers with high-end exposures.

The American Petroleum Institute (API) conducted an occupational benzene exposure survey of petroleum workers using personal air monitoring samples and provided a summary of the results. Refinery operations had the highest number of samples, 10,956, with a mean of 0.147 ppm. Marine distribution had the lowest number of samples, 179, and the highest mean exposure of 0.282 ppm. The other two operations categories were Pipeline, with 1,207 samples and a mean of 0.1241 ppm and Marketing with 1,352 samples and a mean of 0.192 ppm. It does not appear that the data listed included benzene exposure from chemical manufacturing, a source of high-end exposure. The data presented did not include information on 95th percentile or episodic / upset conditions.

As cited in submission and according to ASTDR's ToxFAQs, OSHA has set the PEL at 1 ppm as an 8-hour time-weighted average (TWA) concentration, and a STEL at 5 ppm as a 15-minute TWA for benzene. The NIOSH-recommended exposure limit (REL) and STEL is 0.1 ppm and 1 ppm, respectively.

Children's Exposure

The sponsor focused on pathways and routes of exposure relevant to children and prospective parents and grouped exposures by background sources of exposure and source-specific exposure. Background exposure sources were broken down to two main categories, Ambient Air (outdoor and indoor) and Dietary (food, water and milk). The four source-specific exposures examined were tobacco smoke, gasoline, consumer products and occupational. The primary source that can be directly attributed to the manufacture, process and use of benzene is ambient outdoor air.

Potential benzene exposures were evaluated for those living in close proximity to the highest industrial benzene emitters in urban and rural locations. For typical concentrations, the National Air Toxics Assessment (NATA) database (1996) was queried to obtain predicted concentrations for the counties in which the Top 5 TRI reporting facilities were located. The sponsor does note that the EPA released an updated NATA database using the 1999 emissions inventory, indicating that the predicted ambient air concentrations of benzene nationwide and for the 'all urban' and 'all rural' counties were similar to the 1996 modeled estimates.

3.0. Summary of the Hazard Data

Toxicokinetics of Benzene

Inhalation exposure is the major route of exposure to benzene, although oral and dermal routes are also important. The toxicokinetics (absorption, distribution, metabolism, and elimination) of benzene have been studied in humans and experimental animal species. The available studies indicate that benzene is rapidly absorbed following both inhalation and oral exposure but there are species differences. Benzene is almost completely absorbed from the gastrointestinal tract over a wide range of dose levels in rats and mice. In contrast, several human studies have indicated that the respiratory absorption of benzene is approximately 50%. At high concentrations, benzene metabolism is saturated in rodents, and respiratory excretion of unmetabolized benzene increases. Dermal absorption is less than 1% of the applied dose due to rapid volatilization from intact rabbit/animal skin.

Benzene is rapidly distributed throughout the body regardless of the exposure route. Following oral exposure, the highest concentrations were found in liver and kidneys, intermediate concentrations in blood, and the lowest concentrations in the Zymbal gland, nasal cavity, oral cavity, mammary gland, and bone marrow. Benzene is preferentially stored in fat. Metabolites of benzene are also found throughout the body.

Despite extensive research, the metabolism of benzene to toxic metabolites is still not completely understood. Metabolism of benzene is required for expression of benzene toxicity. Following initial oxidation by CYP2E1 to benzene oxide, however, the benzene metabolic pathway branches to produce several putative toxic metabolites. Several metabolites of benzene may play a role in inducing the toxic effects of benzene, and a combination of several metabolites may be required to cause the full range of benzene-induced toxic responses. Large quantitative differences in the production of putative toxic benzene metabolites have been observed among different animal species. Because few data exist on the proportion of different benzene metabolites produced in humans, there is considerable uncertainty in selecting the most appropriate animal model for humans.

At low exposure levels, benzene is excreted primarily in the urine as sulfate or glucuronide conjugates of phenolic metabolites or as muconic acid (MA). At higher oral doses in rats and mice, greater than 50% was cleared unmetabolized in the breath. Similarly, a small percentage of benzene was exhaled in the breath from inhalation exposure to 10 ppm (32 mg/m³) in rats or mice, but at concentrations greater than 850 ppm (2718 mg/m³) rats exhaled 48% and mice exhaled 14%. Urinary phenol and MA concentrations are correlated with benzene exposure level and have been used to monitor benzene occupational exposure. However, the database for evaluating the relative importance of different excretion pathways in humans is limited. Thus, there is a limited database for comparing the importance of human excretion pathways at varying dose levels with the results of experimental animal studies.

Several different PBPK models have been developed to mathematically describe the uptake, distribution, metabolism, and excretion of benzene. Each of these PBPK models has strong points, and some successfully simulate uptake, metabolism, or excretion in mice, rats, and humans. However, the utility of PBPK modeling to predict the dose of toxic metabolites to target organs in humans is limited by the incomplete knowledge of the toxic metabolites and difficulties in identifying a suitable experimental animal model for humans.

Toxicity Data in Humans

Although a large number of human studies have been conducted on benzene, there are few human studies with reliable estimates of exposure to benzene, and they are also frequently complicated by exposure to other solvents.

The most frequently observed toxic effect of benzene, both in humans and test animal models, is bone marrow depression, which leads to lymphocytopenia, leukocytopenia, thrombocytopenia, anemia, and aplastic anemia. The most sensitive effect observed in humans is the depression of ALC in peripheral blood.

The EPA IRIS RfD and RfC values for benzene are based on an epidemiologic occupational inhalation study by Rothman et al. (1996a). A cross-sectional study of 44 age- and gender-matched controls in a plant in Shanghai, China indicated that five blood parameters, absolute lymphocyte count (ALC), white blood cell count (WBC), red blood count (RBC), hematocrit (HCT), and platelets, were all significantly decreased and mean corpuscular volume (MCV) was significantly increased with increasing benzene exposure. This study showed significant reductions in ALC, red blood cells (RBCs), and platelets in a subgroup of workers exposed to a median 8-hour time-weighted average (TWA) concentration of 13.6 ppm (43.4 mg/m³). In a subgroup of 11 workers exposed to a median 8-hr TWA concentration of 7.6 ppm (24 mg/m³), only ALC was still significantly reduced. Thus this concentration is a LOAEL for benzene immunotoxicity in humans. The findings from this study also indicate that white blood cells were significantly decreased and the mean corpuscular volume was significantly increased in the total exposed group of 44 workers occupationally exposed to a median 8-hour TWA of 31 ppm (99 mg/m³) in comparison to an age- and sex-matched control group. EPA used the data to calculate both a reference concentration (RfC) of 9×10^{-3} mg/m³ for inhalation exposures and, by route-to-route extrapolation, a reference dose (RfD) of 1×10^{-3} mg/kg/day for oral exposures.

Benzene has been shown to produce neurotoxic effects in humans after short-term exposures to relatively high concentrations of the compound. Benzene produces generalized symptoms such as dizziness, headache, and vertigo, leading to drowsiness, tremor, delirium, and loss of consciousness. In an occupational study, workers complained of frequent headaches (usually at the end of the workday), tired easily, had difficulties sleeping, and complained of memory loss. Overall, there is a lack of reliable information on dose-related neurotoxic effects under low-dose chronic exposure conditions in either humans or experimental animal model systems. Neurological

abnormalities in patients diagnosed with aplastic anemia after prolonged exposure to benzene have also been reported. These reports, however, have obvious deficiencies: lack of exposure data, small numbers of subjects, and unknown exposure to other chemicals.

The genotoxic effects of benzene have been demonstrated in numerous studies in humans as well as in *in vivo* and *in vitro* genotoxicity assays. Chromosomal aberrations were consistently detected in peripheral lymphocytes and bone marrow from workers chronically exposed to benzene. Significant increases in aneuploidy and deletions of chromosomes were observed in peripheral lymphocytes of workers exposed to benzene vapor at a mean concentration (TWA) of 30 ppm. Other chromosomal abnormalities noted in human studies include translocations, breaks and gaps. There is also evidence that benzene may be eliciting mutations and oxidative DNA damage in exposed workers. An increase was noted in the frequency of mutations in the “hprt (hypoxanthine-guanine-phosphoribosyl transferase)” loci of peripheral lymphocytes collected from some workers exposed to benzene in an oil refinery. Significant concentration-related increases in 8-OHdG adducts (a marker of oxidative DNA damage) and DNA single strand breaks were observed in peripheral lymphocytes of workers exposed to benzene.

Epidemiologic studies and case studies provide clear evidence of a causal association between exposure to benzene and leukemia, especially acute nonlymphocytic leukemia (ANLL) and, to a lesser extent, chronic nonlymphocytic leukemia as well as chronic lymphocytic leukemia (CLL). Two large series of studies on workers exposed to benzene in Ohio (the Pliofilm study) and China (the NCI/CAPM study) show significant increased risks of acute nonlymphocytic leukemia (ANLL), particularly acute myelogenous leukemia (AML). The study of Pliofilm rubber workers at three facilities in Ohio provides the best published set of data to date for evaluating human cancer risks from exposure to benzene. This study has the fewest reported co-exposures in the workplace to other potentially carcinogenic substances and provides a greater range of estimated exposure to benzene than the cohorts of other studies in which efforts were made to estimate individual exposures.

In the Pliofilm study, a cohort of 1,165 white males employed between 1940 and 1965 and followed through 1981 experienced increased mortality from all leukemias (9 observed versus 2.7 expected; Standardized Mortality Ratio (SMR) = 3.37, 95%CI 1.54-6.41) and AML accounted for most of the increased leukemia (SMR=5.03, 95% CI 1.84-10.97). The last follow-up through 1996 reported five more cases of AML, with an SMR of 3.37, statistically elevated at the highest exposure category. The National Cancer Institute (NCI) and the Chinese Academy of Preventive Medicine (CAPM) conducted an epidemiology study of over 74,000 benzene-exposed Chinese workers employed from 1972 to 1987. Workers came from a total of 672 Chinese factories in 12 cities and were employed in the painting, printing, footwear, rubber, or chemical industries. A statistically elevated risk of all hematological malignancies (RR=2.2, 95% C.I.=1.1-4.2) was observed with air concentrations of benzene less than 10 ppm. A combination of ANLL and myelodysplastic syndrome (MDS) produced a risk of 3.2 (95% C.I. =1.0-10.1).

Hodgkin's lymphoma, appears to be associated with exposure to benzene as well as with hematologic neoplasms in general, which includes AML and related myelodysplastic syndromes.

Benzene has been classified as a known human carcinogen (by EPA, NCI and IARC) based upon evidence presented in occupational epidemiological studies. The inhalation unit risk values of benzene derived by EPA are 2.2×10^{-6} to $7.8 \times 10^{-6} (\mu\text{g}/\text{m}^3)^{-1}$. The range of oral slope factors was determined to be 1.5×10^{-2} to $5.5 \times 10^{-2} \text{ mg}/\text{kg}/\text{day}^{-1}$ and the drinking water unit risk has a corresponding range of 4.4×10^{-7} to $1.6 \times 10^{-6} (\mu\text{g}/\text{L})^{-1}$.

According to the EPA IRIS toxicological assessment for benzene, the evidence regarding reproductive and developmental effects from human studies is limited. Most of the studies consisted of small numbers of subjects, lacked important experimental details, involved (in almost all cases) concomitant exposure to other chemicals, and did not provide monitoring data or qualitative dose-response information. There is also no convincing evidence to indicate that children are more susceptible to the toxic effects of benzene; however, there is evidence that differences in gender and subpopulation susceptibility may exist. Differences in responsiveness to benzene have been observed among species. Absorption studies with humans suggest that absorption by females is higher than by males, and modeling results indicate that females metabolize 23–26% more benzene than men under the same exposure conditions. Differences in benzene metabolism could result in differences in susceptibility, because conversion of benzene to metabolites is necessary for expression of toxicity.

The balance of NQO1 NAD(P)H activity to peroxidase activity in cells may be important in determining benzene toxicity by modulating the concentration of 1,4-benzoquinone, a suspected toxic metabolite. A mutant allele for lack of NQO1 NAD(P)H activity has been reported in a human population at a frequency of 13%. It has been reported that 4% of the British population lack NQO1 NAD(P)H activity. It has also been observed that Chinese workers homozygous for the mutant allele and with high chlorzoxazone excretion (a measure of CYP2E1 activity) had a 7.6-fold higher risk of developing benzene toxicity. Thus, there is good experimental evidence to indicate that benzene-sensitive human subpopulations may exist.

Toxicity Data in Animals

Genotoxicity

In vivo animal studies and *in vitro* assays support the human case reports that benzene is genotoxic. In addition to chromosomal damages, increases in sister-chromatid exchanges have been reported in the bone marrow and lymphocytes of mice and rats. Benzene induced DNA breaks in Chinese hamster ovary cells and intrachromosomal recombination in human lymphoblastoid cell culture independent of metabolic action. Positive results, however, were obtained for gene mutation in the Ames strains of *Salmonella* and for sister-chromatid exchanges in human lymphocyte cell culture only with metabolic activation, suggesting that its metabolites are also involved in the

genotoxic activity. The cytogenetic and mutagenic activities of many of benzene's metabolites have been demonstrated in various *in vitro* systems using bacteria and mammalian cells in culture.

Acute Toxicity

Acute toxicity of benzene has been studied in laboratory animals, mainly rats and mice. The sponsor summarized the available LD50 and LC50 studies. In rats, oral LD50 values range from 810 mg/kg to 10,000 mg/kg. Clinical signs included sedation and narcosis. An inhalation LC50 of 13,700 ppm (44.5 mg/L) with 4-hour exposure of female rats and 10,450 ppm (33.3 mg/L) for mice after 7 hours of exposure. Similar to oral exposure, clinical signs included restlessness, twitching, tremor, changes in respiration, poor coordination, and narcosis. Older studies reported a dermal LD50 >8260 mg/kg in rabbits and guinea pigs. Benzene was a dermal irritant to rabbit ears and damaging to eyes with ocular application.

Repeated Dose Toxicity

Benzene exposure results in adverse noncancer health effects by all routes of administration to test animal species. Hematotoxicity has been consistently reported to be the most sensitive indicator of noncancer toxicity both in limited studies in humans and experimental animals, with bone marrow as the principal target organ. Chronic exposure to benzene results in progressive deterioration of hematopoietic function. Whether the hematotoxic and carcinogenic effects of benzene are due to a common mechanism has not been established. Early biomarkers of exposure to relatively low levels of benzene include depressed numbers of one or more of the circulating blood cell types. A common clinical finding in benzene hematotoxicity is cytopenia, which is a decrease in various cellular elements of the circulating blood manifested as anemia, leukopenia, or thrombocytopenia. Benzene also causes a life-threatening disorder called aplastic anemia in animals as well as humans. This disorder is characterized by reduction of all cellular elements in the peripheral blood and in bone marrow, leading to fibrosis, an irreversible replacement of bone marrow.

Support for the EPA IRIS chronic inhalation RfC and the oral chronic RfD has been provided by the subchronic inhalation study of rats and mice of Ward et al. (1985), which identified a NOAEL of 30 ppm (96 mg/m³) and a LOAEL of 300 ppm (958 mg/m³) in CD-1 mice. This study was selected as a supporting study because it was the experimental animal study with the longest inhalation exposure duration and it provided good dose-response data. The exposure-response relationships for the different hematologic endpoints in male mice are the most sensitive sex/species in this study.

Neurotoxicity

The database for establishing threshold dose levels for neurotoxicity effects is limited; no complete neurological testing has been conducted in animals. Neurological effects of benzene have been observed in animals, but no clear NOAEL could be identified in any

species. The exposure levels used in the neurotoxicity studies were typically high and the exposure durations were short. The longest exposure period was 4 weeks. Significant increases in monoamine neurotransmitters in the brain of rats at doses of 8 and 40 mg/kg/day were observed, but further increases were not observed at 180 mg/kg/day. Reduced milk licking in mice exposed to 100 ppm (319 mg/m³ for 1 or 2 days) has been reported, but grip strength was not affected until exposure reached 1000 ppm (3195 mg/m³). Effects on grip strength, locomotor activity, and Y-maze performance (rapid response) at 0.78 ppm (2.5 mg/m³), have been reported. There is a limited body of evidence indicating that benzene is neurotoxic; however, there are no animal studies that could be used for quantitative evaluation of potential human health risks.

Carcinogenicity

The human data are supported by experimental animal studies which show that benzene exposure increases tumor incidences in multiple species at multiple organ sites. Benzene has been tested for carcinogenicity in rats and mice exposed by several routes, including inhalation, oral administration, dermal application and injection. When administered by inhalation, benzene caused tumors at many tissue sites in rats and primarily lymphoid tumors in mice. When administered orally, benzene caused oral-cavity tumors and Zymbal gland carcinoma in rats of both sexes, skin carcinoma in male rats, Zymbal gland carcinoma, malignant lymphoma, and lung tumors in mice of both sexes, Harderian gland adenoma and preputial gland carcinoma in male mice, and ovarian tumors and mammary gland carcinoma and carcinosarcoma in female mice. Dermal application of benzene caused benign skin tumors in transgenic mice carrying the v-Ha-ras oncogene. Benzene administered by intraperitoneal injection caused benign lung tumors in male mice. The carcinogenic responses of benzene are likely to be due to interactions of various metabolites with DNA. Differences in metabolic capability of different organ tissues in animals as well as in humans are believed to be responsible for the variations in the carcinogenic response to benzene.

Reproductive/Developmental Toxicity

There is a limited body of data available on the developmental toxicity of benzene by the oral route. Decreases in postnatal body weights were observed in a Chernoff/Kavlock screening assay in rats exposed to a single gavage dose of 1300 mg/kg/day benzene administered on gestation days 8-12. Another oral developmental toxicity study exposed 20-22 rats per dose group to 0, 50, 250, 500, or 1000 mg/kg/day during gestation days 6-15. A NOAEL of 250 mg/kg/day and a LOAEL of 500 mg/kg/day, based on decreases in fetal body weight, were reported. However, this study evaluated external malformations only; fetuses were not examined for visceral or skeletal anomalies.

More extensive data exists on the developmental toxicity of benzene by the inhalation route. A considerable number of adequate studies have been conducted in a wide range of experimental animals (rats, mice, rabbits) using intermittent (6 or 7 hours/day) or continuous (24 hours/day) exposure scenarios. Some inhalation studies tested more than one concentration of benzene and demonstrated a concentration response and a LOAEL.

and NOAEL, while others used only one concentration. The single-concentration studies were not considered useful for determining dose-response relationships, but did provide supporting evidence for fetal toxicity. Results of these inhalation developmental toxicity studies are fairly consistent across species and demonstrate that benzene is fetotoxic and causes decreased fetal weight and/or minor skeletal variants (delayed ossification) in rats and mice at concentrations greater than 47 ppm (150 mg/m³).

The developing hematopoietic system in mice also appears to be affected following maternal exposure to benzene, which is consistent with benzene-induced hematologic abnormalities observed in humans and adult animals. Exposure of mice to low concentrations of 5, 10, or 20 ppm (16, 32, or 64 mg/m³) benzene in utero during development has been shown to cause changes in the hematogenic progenitor cells in fetuses, 2-day-old neonates, and 6-week-old adults, with a reported LOAEL of 5 ppm. This effect level is below the LOAEL of 7.6 ppm for hematotoxic effects observed in humans used by the EPA IRIS toxicological assessment of benzene to derive the RfC/RfD; however, the EPA IRIS reports that the biological significance of these effects is questionable because of the experimental design limitations such as, limited hematotoxic endpoints, a lack of consistent responses in different ages of progeny, and a limited number of animals examined. Therefore, these studies were considered as providing only supporting evidence of hematotoxicity.

Multigenerational animal studies on the reproductive toxicity of benzene were not found in the literature; however, some data exists regarding the susceptibility of reproductive organs to the toxic effects of benzene following repeated exposures by both the oral and inhalation routes.

Following subchronic, repeated exposures by the oral route, no ovarian effects were observed in either rats or mice treated for 90-days at doses ranging from 25-600 mg/kg, or in rats treated for 2 years at doses ranging from 25-200 mg/kg. Mice administered benzene for 2 years at doses ranging from 25-100 mg/kg exhibited ovarian lesions ranging from atrophy to neoplasia; however, the incidence of nonneoplastic lesions was not dose related.

Following subchronic, repeated exposures by the inhalation route in rats, rabbits, and guinea pigs, moderate changes in testicular weight at 21,084 mg/m³ (6600 ppm) were observed in rats; slight changes in testicular histopathology at 256 mg/m³ (88 ppm) were observed in rabbits; and slight changes in testicular weight and histopathology at 281 mg/m³ (88 ppm) were observed in guinea pigs. In an adequate subchronic study, groups of 10 male and 10 female rats and mice were exposed by inhalation to concentrations of 0, 1, 10, 30, or 300 ppm (3.2, 32, 96, or 958 mg/m³) for 13-weeks. Testicular weight for the rats was comparable to controls. Reductions in testicular weights with histopathologic alterations, microscopic changes in the ovaries (ovarian cysts), reductions in sperm count, and increased numbers of abnormal sperm were observed in mice at 300 ppm (958 mg/m³). The microscopic changes in the testes and ovaries occasionally appeared at the 10 and 30 ppm groups, suggesting a concentration response. Hematotoxicity also occurred at 300 ppm (958 mg/m³) in mice in this study. The overall

LOAEL for the study was determined to be 300 ppm (958 mg/m³), and the NOAEL was 30 ppm (96 mg/m³).

The effects on the reproductive organs have been characterized in the repeat dose studies. Although studies of reproductive function have not been conducted, it is unlikely that functional effects would occur at doses substantially lower than those affecting the reproductive organs since fertility in male rodents is not affected until the sperm count is reduced more than 90%. In addition, the EPA IRIS toxicological assessment for benzene used a LOAEL of 7.6 ppm (24 mg/m³) based on hematotoxicity from a human occupational exposure study to calculate a chronic RfC and, by route-route extrapolation, the RfD. The reproductive organ effects observed in the available subchronic toxicity studies in animals occurred at doses and concentrations considerably higher than those observed to cause hematotoxicity in humans. EPA considers a two-generation reproductive toxicity study in animals unlikely to yield effects at concentrations substantially lower than those used to derive the EPA IRIS RfC/RfD, and/or significantly impact the risk characterization.

Developmental Neurotoxicity

No definitive studies examining the potential for neurotoxicity in the developing fetus following exposure to benzene were found in the literature. However, a recent study by Lo Pumo et al. (2006) reported changes in several neurobehavioral parameters in neonates when pregnant Sprague-Dawley rats were administered a 0.1 mg/kg solution of benzene by s.c. injection on gestation day 15. At birth, neonatal reflexes (cliff aversion, forelimb placing, bar holding, forelimb grasping, startle response) were different from controls. Starting at 2 months after birth in males, cognitive and motor performance was also altered. Other studies in adult animals by both the oral and inhalation routes have shown effects of benzene on neurotransmitter levels in the brain (See section on Neurotoxicity). Neurotoxicological effects in adult animals may be of particular concern for the developing central nervous system.

Immunotoxicity

Animal data support the findings of damage to both the humoral and cellular components of the immune system has been known to occur in humans following inhalation exposure. Animal studies have shown that benzene decreases circulating leukocytes and decreases the ability of lymphoid tissue to produce the mature lymphocytes necessary to form antibodies. This has been demonstrated in animals exposed for short, intermediate, or chronic periods via the inhalation route. This decrease in lymphocyte numbers is reflected in impaired cell-mediated immune functions in mice following intermediate inhalation exposure to 100 ppm of benzene. The impaired cellular immunity after benzene treatment was observed both *in vivo* and *in vitro*. Mice exposed to 100 ppm for a total of 100 days were challenged with 104 polyoma virus-induced tumor cells (PYB6). Nine of 10 mice had reduced tumor resistance resulting in the development of lethal tumors. In the same study, lymphocytes were obtained from spleens of benzene-treated mice and tested for their immune capacity *in vitro*. The results showed that two other

immune functions, alloantigen response (capacity to respond to foreign antigens) and cytotoxicity, were also impaired. Similar effects were noted in mice exposed to benzene via the oral route for intermediate time periods, and in rats and mice exposed for chronic time periods. A decrease in spleen weight was observed in mice after acute-duration exposure to benzene at 25 ppm, the same dose levels at which a decrease in circulating leukocytes was observed. Similar effects on spleen weight and circulating leukocytes were observed in mice exposed to 12 ppm benzene 2 hours/day for 30 days. These results indicate that exposure to benzene, whether oral or inhaled, adversely affects the immune response.

The ATSDR has used immunotoxicity studies in animals as the basis of two MRLs. The acute-duration inhalation MRL was based on a study showing decreased mitogen-induced blastogenesis of B-lymphocytes following exposure of mice to benzene vapors at a concentration of 10 ppm, 6 hours/day for 6 days. The intermediate-duration inhalation MRL was based on a study showing delayed splenic lymphocyte reaction to foreign antigens evaluated by in vitro mixed lymphocyte culture following exposure of mice to benzene vapors at a concentration of 10 ppm, 6 hours/day, 5 days/week for a total of 20 exposures.

4.0 Summary of the Sponsor's Risk Characterization

Background

The sponsor's risk characterization combined information in the hazard and exposure assessments to assess the potential risks to children and prospective parents from exposures to benzene. It included an analysis of the noncancer and cancer risks from benzene by using the same key studies (human occupational epidemiology studies) and critical effects (ALC, AML) on which the EPA IRIS values were based. The sponsor used an EPA default (linear) approach using a Reference Dose (RfD) and Cancer Slope Factor (CSF), and a margin of safety (MOS) approach that used a point of departure (POD).

For non-cancer, the sponsor used the EPA RfD to calculate hazard quotients (HQs). HQs were calculated as the ratio of the estimated exposure to the RfD. According to the sponsor, exposures resulting in an HQ that is less than 1 are unlikely to result in non-cancer adverse health effects. Exposures were averaged over the duration of the exposure period. All exposures quantified in the sponsor's exposure assessment were calculated as absorbed doses. The sponsor calculated high and low HQs for each exposure scenario and corresponding age groups for children's and adults' exposures. The high risk estimate was based on EPA's RfD (adjusted to absorbed dose). The low risk estimate was calculated by dividing exposures by the sponsor's alternative #3 RfD (discussed below). For carcinogenic endpoints, the sponsor calculated risk estimates by multiplying the exposure by the (CSF). This estimate of risk was interpreted as the probability of increased incidence of cancer in a lifetime. The sponsor's MOS approach compared a calculated exposure to a POD; the MOS represented the ratio between the POD and the exposure dose.

The sponsor's risk characterization used a range (by a factor of 30) of reference values for benzene, as opposed to the use of a single point estimate for characterizing risk, as with EPA's benzene IRIS assessment (by a factor of 3). The sponsor argues that a broader range of risk estimates provides a better perspective because a more narrow range contains a large degree of uncertainty, usually only reflecting the upper end of the conservative range. The EPA IRIS RfC and RfD were based on benchmark dose modeling (BMD) of the ALC data. The sponsors argue that unlike the presence or the absence of a tumor, ALC is a continuous endpoint; that is, there is a range of normal ALC values and thus no single clear definition for an adverse level. Therefore, the sponsors believe a range of risk estimates is a better approach. The sponsors also offer arguments against the uncertainty factors applied to the EPA RfC/RfD.

All background pathways of exposure, including inhalation, ingestion, and dermal contact, were added together by the sponsor to determine a total average daily dose for each age bin. Exposures resulting from gasoline sources were aggregated with background exposures. Exposures for smokers and their children were made separately from benzene exposures derived from other background or source-specific sources. Typical and high end exposures for almost every exposure scenario were estimated. Aggregate exposures were calculated for the typical and high end exposures by summing the respective typical and high end exposure estimates from the inhalation, ingestion, and dermal pathways.

According to the sponsor's exposure assessment, indoor air (in the home) is the predominant pathway and may contribute upwards of 70%-80% of aggregate exposures for children in non-smoking households. The sponsor reports that concentrations of benzene in Alaskan homes with attached garages are significantly higher than concentrations of benzene in homes in the continental U.S. (CONUS). For children in a smoking household, the background indoor air contributes to approximately 50%-60% of total exposures.

For carcinogenic effects, the sponsor calculated exposures by averaging the total cumulative dose over a lifetime. The lifetime average daily dose was calculated as a time-weighted value over a 70-year lifespan using the average daily dose (ADD) and the applicable exposure duration for each group.

According to the sponsor, not enough is known about the mechanism of action of benzene for the toxic endpoint (e.g., hematopoietic toxicity) to choose a defensible critical dose measure to form the basis of a PBPK-based risk assessment. Therefore, the sponsor's risk assessment was conducted using absorbed doses of benzene as the critical dose metric. A PBPK model for benzene was used, however, to calculate the dose of benzene to an infant via breast milk from an exposed mother

With respect to differences in sensitivity to the toxic effects of benzene between adults and children, the sponsor argues against the application of any children's sensitivity adjustment factors to the current RfD, CSF, and any PODs derived in their risk

assessment. The sponsor states that there is no consistent evidence in the published medical or scientific literature on the myelosuppressive/hematotoxic effects of various chemotherapy agents in children and adults to support the existence of an age-related difference in sensitivity.

Results of Non-Cancer Risk Calculations

When using the EPA IRIS RfD, the sponsor calculated HQs of 1 for children <1 year old and 1 to <2 years of age exposed to high end background sources of benzene (all routes aggregated) and for adolescents and adults who smoke cigarettes. When using the sponsor's alternative # 3 RfD, no exposure scenarios exceeded an HQ of 1. HQs for an infant ingesting human breast milk from an occupationally exposed mother were the same as HQs for a nursing infant whose mother was not occupationally exposed.

The sponsor also estimated MOSs for noncancer effects. The POD used for the noncancer MOS calculation was 0.5 mg/kg/day (absorbed dose), based on reductions in ALC, with a No Observed Adverse Effect Concentration (NOAEC) of 1 ppm. The MOSs were estimated for different exposure scenarios/sources and for aggregated exposures for each age group (adults, children, in-home inhalation from living in homes in the CONUS and Alaskan homes with attached garages). For aggregate exposures, the MOSs ranged from approximately 100-2,100. The MOSs for smoking were estimated to range from approximately 50-100.

Results of Cancer Risk Calculations

The sponsor generated potential excess cancer risk estimates for males and females based on lifetime average daily doses using the range of CSFs provided by the EPA IRIS assessment and using the lower bound CSF calculated by Crump (1996). Using the upper-bound linear model CSF, background aggregated exposures (from urban and rural, typical and high end), were shown by the sponsor to be associated with excess cancer risks greater than 1×10^{-5} . Using the lower-bound linear model CSF, background aggregated exposures (from urban and rural, typical and high end), were shown by the sponsor to be associated with excess cancer risks less than 1×10^{-6} . Smoking tobacco (direct mainstream smoking) was shown by the sponsor to lead to excess cancer risks greater than 1×10^{-4} .

The sponsor also calculated HQs and potential excess cancer risk estimates for indoor (in-home) air, comparing typical and high end estimates from the CONUS. The HQ for the <1 year old ranges from 0.07 (low HQ estimate using the sponsor's alternative #3 RfD) to 2 (using EPA's IRIS RfD). Using EPA's RfD, the only age group that has an HQ higher than 1 is the < 1 year old age group. Using the sponsor's alternative #3 RfD, all HQs are below 1 for both Alaska and the CONUS. Using the upper-bound linear model CSF, estimated potential excess cancer risks do not exceed 1×10^{-4} for Alaskans. Using the lower-bound nonlinear model CSF, estimated potential excess cancer risks for Alaskans were predicted by the sponsor to be 4×10^{-7} . HQs for adults exposed to indoor air from homes in the CONUS (typical and high end) and Alaskan homes do not exceed 1

using EPA's RfD, and were reported by the sponsor to be significantly less than 1 using their alternative #3 RfD.

The sponsor's assessment concluded that smoking was the predominant exposure scenario contributing the most to overall benzene exposures and HQs for typical exposures for 16-19 year old adolescents. Refueling a car and riding in a car contributed the least to children's aggregate benzene exposures and HQs. Of the remaining sources of benzene exposures, indoor air contributed the largest fraction. For all age groups, the sponsor's calculations showed that the HQ associated with active smoking was significantly greater than all other exposures combined (aggregated background sources: environmental tobacco smoking, refueling a car, and active smoking in adolescents and adults). The sponsor concluded that smoking is the dominant source of benzene exposures, resulting in high HQs and potential health risks.

Estimates of MOSs for cancer for lifetime daily doses for males and females were also calculated by the sponsor for each exposure source and for aggregate exposures. The POD used for the cancer calculation was 0.05 mg/kg/day (absorbed dose), based on elevated risk of AML, with a European Union critical exposure level (CEL) of 0.1 ppm. The cancer MOSs for aggregate exposures for all background sources of exposure ranged from approximately 30 to 160. The MOS for smoking was estimated at approximately 7.5. Predicted MOS associated with in-home inhalation exposures for children living in Alaskan homes with attached garages was approximately 25 for cancer.

5.0 Summary of the Sponsor's Data Needs Assessment

The sponsor considers the exposure assessment to be fully adequate to demonstrate exposures to benzene from anticipated sources. The sponsor suggests that any future exposure data will likely be lower than the data used in this exposure assessment because significant reductions in benzene emissions and exposure levels have occurred and are expected to continue as a result of extensive occupational and environmental regulations and risk management efforts currently underway.

The sponsor considers all Tier 1 toxicity studies specified in VCCEP to have been completed. Additionally, the sponsor believes that there are extensive hazard data for benzene that generally cover all of the Tier 2 toxicity tests and most of Tier 3 toxicity tests. The sponsor identifies a Tier 2 toxicity data gap, a two-generation reproductive toxicity study. However, the sponsor argues that existing studies evaluating benzene's effects on reproductive performance and fertility in animals showed limited effects in both female and male rats, and in male mice; and according to the sponsors, data in humans for this endpoint is equivocal. The sponsors acknowledge that some additional information could be gained from a two-generation reproductive toxicity study, but argue that its usefulness would be limited. The sponsor points out that most of the existing risk assessments and risk management actions for benzene are based on the extensive human health effects database which has established hematological endpoints and acute myelogenous leukemia as the critical effects for not only the current VCCEP assessment, but other existing assessments of benzene (IRIS, IARC, EU, ACGIH, etc.). Since

exposures are anticipated to continue to exhibit a downward trend, the sponsors do not believe there is adequate rationale or justification for conducting a 2-generation reproductive toxicity study in experimental animals at this time.

6.0 EPA Response to the Data Needs Assessment

For the exposure assessment these are areas of the assessment that EPA believes have not been addressed, lack data, analyses or transparent presentation. EPA believes that these areas can significantly affect the exposure assessment of benzene.

EPA notes that very limited information was given on the manufacture, process or use of benzene. The submission mentioned three primary processes cited from ATSDR, catalytic reforming, catalytic dealkylation, and steam cracking and provided estimates of the percentages of total production; however, the submission did not differentiate processes in which benzene was intentionally manufactured (e.g. steam cracking) or was produced as a by-product (e.g. catalytic reforming). The assessment does not address emissions from the three primary processes nor does it address benzene emissions that can occur under current regulations, such as the permitted 45-day allowance for repair of cooling water leaks, or emissions that are not covered by current regulations, such as decoking. Finally, the submission does not address emissions from events / upsets, especially from the manufacture of the chemical.

EPA concludes that the environmental fate of benzene was not adequately addressed for a risk assessment, especially in the areas of persistence and partitioning. Of particular concern are benzene emissions to water, as assessment assumes the chemical will all partition to air. The assessment characterizes the water solubility of benzene as "low-moderate"; however, EPA would characterize the solubility as "moderate". Also, the Henry's Law constant is characterized as "High" and EPA would characterize it as "Moderate". Whereas monitoring data may suggest benzene is most commonly found in air, Level III Fugacity modeling shows that water can be significant sink for benzene, once it is discharged into water (e.g., from cooling water leaks).

In the High Production Volume program, the Office of Pollution Prevention and Toxics accepts the results of a Level I fugacity model, but makes it clear that results of a Level III fugacity model are preferred. The submission should include the results of Level III fugacity modeling. The submission should include not only model results, but also the degradation half-lives and chemical properties used to run the model. Level I fugacity modeling considers only equilibrium partitioning, ignoring all types of degradation. Level III fugacity modeling includes degradation, advection (physical movement of a substance), atmospheric deposition, etc.

Level III fugacity results are typically quite different and may show that the model does not predict that all of the chemical will partition out of water at steady state. In fact, the Level III results suggest that water, soil, and sediment are the major compartments for these types of chemicals when equal, continuous emissions to air, water, and soil occur. This highlights the importance of data on emissions as well as degradation rates for all

major compartments. EPI Suite™ makes Level III fugacity calculations and is readily available at: <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

The submission states that benzene biodegrades in groundwater (although no reference is provided), but does not address the removal of benzene in sewage treatment or drinking water treatment plants. Biodegradation is a process that can significantly affect environmental fate and exposure, and it is important to include both along with references.

EPA also notes that there was an over dependency on the information supplied by the TEAM study with the assessment's focus on indoor benzene exposure and in minimizing effects of personal exposure to those that lived by fixed sources. As stated in the Federal Register for VCCEP, "*Similarly, a complete reliance on the biomonitoring data for an exposure assessment, given the quality concerns raised by stakeholders, would be insufficient*" and that "*Sponsors will bear a special responsibility in defining and describing the essential exposure issues associated with each chemical.*" (Vol. 65, No. 248, pg. 81711) It is the responsibility of the sponsor to fully address ambient air exposures, especially in areas that pose a high and cumulative risk, such as Texas, versus relying on portions of the TEAM study in negating these effects.

There were also discrepancies in the use of 1996 NATA data measurements in comparison to top benzene emitters using 2003 TRI data in the development of typical urban and rural exposures. All of the urban and rural facilities not controlled by the sponsors, (Holcim, US Sugar and GP) were not even emitting benzene in 1996. The two top urban sponsors listed on page 103 of submission, US Sugar Corp in Palm Beach County, Florida and the Holcim plant in Michigan had no reported emissions of benzene in 1996. The top rural benzene source, Georgia-Pacific in Bedford County, Virginia had no TRI benzene releases in 1996. However, the 1999 emissions inventory would include reported benzene emissions from U.S. Sugar, who opened a 600,000-ton per year refinery in 1998. It would be of interest to note if ambient air concentrations did increase in this area as to whether the NATA is an accurate predictor of ambient air concentrations of benzene. The data used to represent the typical urban and rural concentrations was in error and used for all other estimates of outdoor ambient air exposure to children. It is also not transparent that the NATA data measurements accurately depict ambient air concentrations of benzene, especially with fluctuating levels and the chemicals ½ life.

Finally, EPA notes that the sponsor excluded consideration of available data from the ongoing monitoring programs implemented as a result of the Texas air quality study conducted in 2000. Texas increased Auto GC's for ambient air measurement, expanding the number from three to a dozen in Harris County. Texas followed in 2002 with the mass monitoring of both continuous and episodic emissions from sources of Highly Reactive Volatile Organic Chemicals (HRVOC). (TCEQ, Texas Commission on Environmental Quality, "Central Registry," "Speciated Emissions Inventory," "Air Emission Event Reports," 2004, "PCQ", 2005; available on TCEQ website, <ftp://ftp.tnrcc.state.tx.us>)

All Tier 1 toxicity studies and most of Tier 2 toxicity studies have been conducted. For Tier 1, acute toxicity studies, mutagenicity studies, and numerous repeat-dose toxicity studies have been conducted. Effects on reproductive organs have been tested in studies with longer-term administration of benzene. For Tier 2, numerous repeat-dose toxicity studies, adequate developmental toxicity studies by the inhalation route in several species, mutagenicity studies, immunotoxicity studies, and metabolism and pharmacokinetic studies have been conducted. For Tier 3, numerous chronic/carcinogenicity studies in multiple species and by multiple routes of exposure have been conducted.

EPA has identified several data gaps for toxicity for Tier 2: a developmental toxicity study by the oral route, and a two-generation reproductive toxicity study; and, for Tier 3: a developmental neurotoxicity study, and a complete neurotoxicity screening battery in adult animals.

For developmental toxicity by the oral route, limited data are available. Only two studies were located; a developmental toxicity screening assay using a single, high dose; and a second multiple-dose prenatal developmental toxicity study that assessed only limited endpoints. However, adequate data for developmental toxicity by the inhalation route are available in multiple species. Because the developmental effects observed in the animal studies occurred at doses and concentrations considerably higher than those observed to cause hematotoxicity in humans, the most sensitive endpoint used for the derivation of the EPA IRIS RfC/RfD, EPA believes it is unlikely any additional developmental toxicity studies would yield effects at concentrations substantially lower than those used to derive the EPA IRIS RfC/RfD, and/or significantly impact the risk characterization. Therefore, EPA does not consider additional developmental toxicity studies a data need for VCCEP at this time. Members of the Peer Consultation Panel did not indicate the need for any additional prenatal developmental toxicity studies from the VCCEP tiers.

The effects on the reproductive organs have been characterized in the repeat dose studies. Ward et al. (1985) conducted an adequate subchronic, repeat-dose study in which reductions in testicular weights with histopathologic alterations, microscopic changes in the ovaries (ovarian cysts), reductions in sperm count, and increased numbers of abnormal sperm were observed in mice at 300 ppm (958 mg/m³). Supporting evidence of toxicity following exposure to benzene comes from a number of subchronic, repeat-dose toxicity studies conducted by both the inhalation and oral routes in a wide range of animals. Although studies of reproductive function have not been conducted, it is unlikely that functional effects would occur at doses substantially lower than those affecting the reproductive organs since fertility in male rodents is not affected until the sperm count is reduced more than 90%. In addition, the EPA IRIS toxicological assessment for benzene used a LOAEL of 7.6 ppm (24 mg/m³) based on hematotoxicity from a human occupational exposure study to calculate a chronic RfC and, by route-route extrapolation, the RfD. The reproductive organ effects observed in the available subchronic toxicity studies in animals occurred at doses and concentrations considerably higher than those observed to cause hematotoxicity in humans. EPA considers a two-generation reproductive toxicity study in animals unlikely to yield effects at

concentrations substantially lower than those used to derive the EPA IRIS RfC/RfD, and/or significantly impact the risk characterization. Therefore, EPA does not consider a two-generation reproductive toxicity study a data need for VCCEP at this time. Members of the Peer Consultation Panel also stated that a 2-generation study was not warranted.

For neurotoxicity, a complete neurological testing of benzene in either young or adult, animals has not been conducted. Benzene has been shown to produce neurotoxic effects in experimental animals after short-term exposures to relatively high concentrations of the compound, and neurotoxic effects have been observed in epidemiology studies. A limited number of studies in adult animals by both the oral and inhalation routes have shown effects of benzene on neurotransmitter levels in the brain. Neurotoxicological effects in adult animals may be of particular concern for the developing central nervous system. However, several experimental deficiencies for this endpoint prevent a quantitative evaluation of risk to humans. Overall, there is a lack of reliable information on dose-related neurotoxic effects under low-dose chronic exposure conditions in either humans or experimental animal model systems. This remains an area of uncertainty. Further investigation of these effects could reveal neurotoxic effects to be of concern to human health. Therefore, EPA has identified an adult neurotoxicity screening battery and a developmental neurotoxicity study as Tier 3 data needs.

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