

Response to Comments on Toxicological Issues related to Benzene submitted by the American Petroleum Institute (API) (Set 1).

Comment 1: "We recognize that the supporting document for prioritization of benzene was developed within the context of a restrictive time frame, and given the charge of the Children's Environmental Health Protection Act, we recognize that an exhaustive review of the subject matter is not required. However, by failing to reference or discuss sections of the benzene literature that do not support special sensitivity of the child, this document deviates from an objective review and critique of the subject matter that would provide a basis for scientifically sound risk management actions under the provisions of the Act.

"In Section V. A. b. the author does not provide citations to the primary literature to support the assertions made regarding developmental and reproductive toxicity. Instead, the reference provided is to another OEHHA document (OEHHA, 1997). This document is a draft which apparently was never finalized. Although the document is available on the State of California website, the interested reader needs to know to look under the Proposition 65 section of the OEHHA site in order to find it. Having found it, the reader must browse the document and attempt to ascertain the specific citation that is offered as support for the position posited in the Children's Health prioritization document. This same problem occurs to a lesser extent with the citation to OEHHA, 2000a. Although these documents contain references to peer reviewed publications, these documents have not themselves been subjected to peer review. This is especially problematic when large sections are quoted in support of the author's position."

Response 1: The commenter is correct that OEHHA developed this document in a restricted timeframe, and the document does not provide an exhaustive review of the subject matter. For these reasons, OEHHA utilized, where possible, previous efforts to review the benzene literature during development of the Public Health Goal for benzene in drinking water (OEHHA, 2000) and during the development of information on benzene for the Developmental and Reproductive Toxicant identification under Prop 65 (OEHHA, 1997). The draft was not intended as a selective review of the literature, as both positive and negative epidemiological studies were described. OEHHA thanks the API for identifying additional studies not cited in

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

the draft. Analysis of these will be included when the prioritization document is finalized. It should be noted that in all occurrences in the draft, OEHHA described the evidence of benzene and childhood leukemia as suggestive. OEHHA believes that a causal relationship would be difficult to establish at this time.

Comment 2: "On Page 4 in the 2nd paragraph under Section IV. B. the author addresses the problem that the majority of childhood leukemia are acute lymphocytic leukemias (ALL) but that the most common form of leukemia associated with benzene exposure is Acute Non-Lymphocytic Leukemia (ANLL). This dichotomy is expressed as a difference of opinion among experts as to the etiology of adult and childhood leukemias. We recognize that OEHHA has taken the position that lymphocytic leukemias may result from exposure to benzene. However, most experts agree that there is little or no support for this position and that benzene-induced leukemia is of the ANLL type (Snyder and Kalf, 1994; Irons and Stillman, 1996). Crump (1994) demonstrated that the dose response between benzene exposure and subsequent leukemia mortality in the Pliofilm cohort was due to ANLLs and that inclusion of other leukemias merely diluted the dose response. Therefore, there appears to be no dose response relationship for other leukemias in the Pliofilm cohort, which has been the basis for most benzene standards."

Response 2: There is little doubt that ANLL is the most common tumor associated with occupational exposures to benzene. However, there is evidence to suggest that benzene is associated with other forms of leukemia as well (reviewed in OEHHA, 2000). Many epidemiological studies indicated significant dose-response relationships between benzene exposure and total leukemia (Ott et al., 1978; Rinsky et al., 1987; Wong, 1987; Paxton et al., 1994a; Hayes et al., 1997). Two epidemiological cohorts identified as providing the most useful data for this assessment exhibited increased relative risks for non-ANLL leukemias. In the Pliofilm Cohort an increased relative risk (RR) of 1.9 was observed for non-ANLL (Crump, 1994), notwithstanding the commenter's emphasis on the ANLL result in this study. Also, a RR of 2.0 was reported for non-ANLL in the recent, large retrospective cohort study (Hayes *et al.*, 1997) of benzene-exposed workers in China (74,828 benzene-exposed workers,

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

and 35,805 controls). The study was done jointly by U.S. National Cancer Institute and the Institute of Occupational Medicine, Chinese Academy of Preventative Medicine. The increased RR for non-ANLL was consistent across all industries (Hayes *et al.*, 1997). Hayes *et al.* (1997) also reported that benzene-exposed workers in some industries in the Chinese cohort had significantly elevated relative risks of non-Hodgkin's lymphoma compared to unexposed workers.

Also, benzene is a multi-site carcinogen in male and female rats and mice, is immunosuppressive in humans (Ward *et al.*, 1996; Rothman *et al.*, 1996) and rodents (Rozen *et al.*, 1984), and alters both myeloid and lymphoid cell lineages (Farris *et al.*, 1997; MacEachern *et al.*, 1992).

Comment 3: "On Page 8 in the 1st paragraph under Section IV. C. the author refers to "mounting evidence that key genetic events related to childhood leukemia occur in the developing fetus.", but the nature of the evidence is not stated. It is clear that the presence of gene fusion products in Guthrie card blood spots from children with childhood leukemia indicate a prenatal origin of that genetic lesion (Gale *et al.*, 1997; Wiemels *et al.*, 1999). However, no studies to date have established a link between the parents of those children and benzene exposures. The sentence which follows the above quote (about the greater exposure to airborne pollutants in children than adults) is true due to the factors mentioned but is a nonsequitor to the preceding statement about prenatal leukemia; these statements should be separated from one another."

Response 3: The references describing the data on gene fusion products noted in the comments are the data to which the draft refers. These are important studies that provide biological plausibility by linking early life genetic damage to the development of childhood leukemia. The commenter is correct that no data specific to benzene and these gene fusion products are available. In order to better express the intent of the original author, a paragraph break will be inserted between these two sentences to separate out the information related to differential exposure between children and adults.

Comment 4: "In the last sentence of the 1st paragraph of Section IV. C. the author states that a child's hematopoietic system may be vulnerable to leukemia since it is undergoing maturation. However, the fetal hematopoietic system exists exclusively in the liver until the 5th month of gestation and until birth the granulocytic portion of the fetal bone marrow derived hematopoietic system is largely arrested at the GM-CFU (progenitor cell) stage. Therefore, this critical cell compartment is not undergoing clonal expansion or differentiation until near the time of birth. Near the end of fetal life and during very early childhood there is a period of rapid maturation with the formation and expansion of the neutrophil compartment during which the proliferation rate is significantly higher than in adults (Wintrobe, 1993). However much of the mitotic activity is in fully committed cells that are incapable of clonal expansion.

"Although it may be true that some organ systems in the young child are developing and maturing at a rate significantly higher than that of adults, e.g., neurological systems, the hematopoietic system may be unique. In this system the adult hematopoietic system undergoes a series of clonal succession events in which a pluripotent stem cell undergoes rapid differentiation and proliferation in order to meet the needs of daily cell turnover (Irons and Stillman, 1996). Thus, the adult hematopoietic system is one of the few which continually undergoes rapid cell division through adulthood. Thus, while many organ systems (e.g. CNS, immune) have profound differences in cell turnover and functional capacity between children and adults, the overall disparity between adult and children's hematopoietic systems does not seem to justify the need for an additional safety factor to be applied to regulatory actions."

Response 4: OEHHA agrees that the hematopoietic system is unlike other solid organ systems. Rapid cell turnover in the bone marrow occurs throughout life. The commenter draws attention to the fact that the bone marrow compartment of the hematopoietic system is relatively inactive during fetal life, and that various elements of the system do not reach their adult configuration until after birth and the earlier stage of childhood. We find this to be consistent with the statement that a child's hematopoietic system may be vulnerable to leukemia since it is undergoing maturation. Since the hematopoietic system exists in an

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

undeveloped state in the fetal and early postnatal phases, it is necessary that a series of major changes in anatomy, cellular composition, physiology and control mechanisms be achieved during childhood, between the early postnatal period and adulthood. These major architectural and functional changes present a potential window of sensitivity since processes are occurring which are not present in the more stable adult configuration. These changes are quite apart from and in addition to the necessity of growth in cell number in concert with the overall increase in body size during this period.

The draft discusses early-life hematopoiesis in the fetal liver of animals (page 15, Section V.C.) but does not discuss the human case. The draft will be revised to discuss *in utero* hematopoiesis in humans as well. However, as stated in the draft (Section V.C.c.), *in utero* exposure to benzene in animals (at a time when the liver is the site of hematopoiesis) resulted in permanent alterations to the hematopoietic system. "Evidence in animals suggests that exposure to benzene *in utero* alters maturation of lymphocytes, erythrocytes and granulocytes (OEHHA, 1997). The consequences of *in utero* exposure to benzene can be detected as alterations in cell population numbers and functional properties that in several cases persist into adulthood (Keller and Snyder, 1986; Keller and Snyder, 1988; Corti and Snyder, 1996)." Alterations of hematopoiesis and clonal selection are believed to be important mechanisms involved in benzene-induced carcinogenesis (Irons and Stillman, 1996; Smith and Fanning, 1997).

Comment 5: "On Page 10 The role of metabolism in the toxicity of benzene is discussed. The author acknowledges that low levels of CYP2E1 in the fetus and during early life would result in less metabolism of benzene to toxic metabolites during this period. The statement is made that a detailed study of other enzymes is necessary in order to predict the effects of exposure to benzene in early life. Enough information to make some predictions, however, is provided in the main body of the report, "Prioritization of Toxic Air Contaminants under the Children's Environmental Health Protection Act" to which the benzene review is appended. In Table 5 of that document CYP2E1 is reported to be very low in the fetus and neonate rising rapidly in the first year of life to a level still below the adult level. Sometime between year one and year 15,

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

possibly at puberty if the analogy with rodents holds, adult levels are reached. This indicates that at least the fetus and infant will metabolize benzene at a slower rate than adults. Lower levels of CYP2E1 are also important because this enzyme is also involved in the metabolism of phenol to hydroquinone (Snyder and Hedli 1996). In summary, lower levels of CYP2E1 activity in the fetus and infant suggests a decrease in susceptibility to benzene toxicity in this period of development.

"Some information about the development of other enzymes important in the metabolism of benzene is also provided in the main body of the report Phase II enzymes are generally decreased in the fetus and early infant, but with glucuronidation and sulfation reactions rising to adult levels by 2 and 6 months of age, respectively. This would result in less protection from metabolites such as phenol or hydroquinone that reached the fetus through the placenta or was formed in situ. Also glutathione transferase mu which accepts benzene oxide as a substrate reaches adult levels within 3-6 months. A quick search of the literature revealed no information on early levels of NADPH Quinone oxidoreductase (NQO1, DT-Diaphorase) in human. However studies in the rodent liver have demonstrated that DT-diaphorase activity is very low in the fetus but rise to adult levels within 1 to 4 weeks after birth (Hommes, *et al.*, 1978; Wallin, 1989)

"So while there is a clear window of time during which the fetus and infant have a low ability to conjugate potentially toxic metabolites of benzene, this window represents a relatively short period of vulnerability. Also, during gestation, the fetus is protected by the ability of the mother to metabolize and detoxify benzene. The result is that the effective exposure of the fetus is smaller than that of the mother. Although the overall balance of toxication and detoxication in the young child or fetus is not likely to be identical to that of the adult or older child it is unclear that metabolism considerations result in a marked disadvantage during gestation and childhood. The discussion of xenobiotic metabolism in the main body of this document supports the position that the period of greatest enzymological disparity between children and adults is confined to a relatively short period during gestation and the first year of life.

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

"From a metabolic perspective the risk of toxicity (genetic or otherwise) can be expected to be as great in the adult as in the child. Myeloperoxidase which can activate phenolic metabolites of benzene such as hydroquinone, to toxic quinones has been established to exist in human CD34+ cells in adult bone marrow which are the origin of all myeloid cell types (Strobl *et al.* 1993). However, bone marrow NQO1 activity which can detoxify quinones exists in the marrow stromal cells. This leads to a situation of a high toxication/detoxication ratio in cells from which all ANLLs arise. The implications of this situation has been reviewed in Ross *et al.* (1996). The relevance to the relative risks of ANLL arising from adult or childhood exposure to benzene is that, with high MPO activity and no NQO1, the adult cell compartment that gives rise to benzene induced leukemia is effectively at maximum risk metabolically. The MPO/NQO1 ratio is unlikely to be any higher in children unless one hypothesizes MPO levels higher in the fetus or children than in adults, and here is no experimental or theoretical foundation for this hypothesis."

Response 5: OEHHA thanks API for this analysis. OEHHA still contends that a detailed study is needed to predict the metabolism and distribution in the fetus and infant relative to the adult. An important factor that the commenter alluded to is the transfer of maternal-form metabolites to the fetus (Ghantous and Danielsson, 1986), which could be important if detoxification mechanisms such as NQO1 are not operative. Although fetal or neonatal oxygenase activities are underdeveloped, the corresponding Phase II (detoxification) enzyme systems are even less active relative to the adult. Illustrations of this point can be found in descriptions of enzyme activities, toxicity and DNA adduct formation in fetal or neonatal rodents cited in the SB25 summary on benzo[a]pyrene and other PAHs (e.g, York *et al.*, 1984).

With respect to the comment on NQO1 expression in adult bone marrow (citing Ross *et al.*, 1996), recent work by Dr. Ross, which he presented at the March 2001 Society of Toxicology meeting in San Francisco (Toxicologist 60(1):2129), indicated that NQO1 is expressed in bone marrow endothelial cells. Dr. Ross noted that these cells are not readily aspirated, which may be the reason why low NQO1 activity in the marrow was originally reported. Moreover, there are important functional polymorphisms in NQO1 that are induced by benzene to widely varying degrees.

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

Finally, kinetic differences in metabolism and detoxification are but one type of factors influencing relative toxicity in infants and children versus adults. Pharmacodynamic differences also play a role. If a target is only present or is hypersensitive during a specific developmental window, then kinetic differences may not be the predominant factor determining toxicity. This is certainly the case for certain developmental toxicants. As noted in the response to comment 4, the maturing hematopoietic system undergoes major physiological and architectural changes which the adult organism does not experience. Thus windows of susceptibility present during maturation are not present in the adult organism.

Comment 6: "Another point to consider is that for mechanisms of childhood leukemia induction via preconception exposure of the father or mother, the issues of fetal metabolic capacity and pharmacokinetics are moot. If it were true that preconceptional exposure of either parent could result in an increased risk of subsequent leukemia in their children, this is not an issue of disparate effects on children and does not justify the need for additional regulation of childhood exposures. The effect on the sperm or ovum will be governed by adult physiologic and metabolic processes. Those differences that do exist between children and adults are not involved in this putative origin of childhood leukemia."

Response 6: As noted above, the available evidence is suggestive for associations between benzene and preconceptional carcinogenesis. OEHHA believes that a causal relationship would be difficult to establish at this time. However, if a causal relationship were established between preconceptional exposure to a carcinogen and increased rates of cancer among offspring, then cancer potency estimates based on adult occupational exposures alone may not capture the full adverse health effects associated with exposures to that chemical since the endpoint of cancer in the offspring is not evaluated in occupational epidemiology studies. The wording of the legislation directing the performance of this evaluation is evidently concerned with health effects in children which may be more severe, different in kind, or at lower doses than those seen in adults. No concern is expressed as to the exact timing or life stage at which the precipitating exposure might occur, or the mechanism by which such an effect might be caused.

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

Comment 7: "In section V.A.b., Developmental and Reproductive Effects, the only source cited is the OEHHA review prepared for the Proposition 65 DART Committee (OEHHA, 1997). The majority of this section consists of lengthy quotes from the OEHHA review. As stated in the general comments above the use of this unpublished review document makes a critical evaluation of the present document difficult."

Response 7: OEHHA developed this draft in a restricted timeframe and did not undertake an exhaustive review of the subject for the purposes of the prioritization effort. For these reasons, OEHHA utilized, where possible, previous efforts to review the benzene literature (OEHHA, 1997; 2000). The review documents cited have been readily available to the public for some time. If the commenter has been unable to obtain a copy of the document they refer to in this comment, it may be obtained from the OEHHA Web site:

<http://www.oehha.ca.gov/prop65/pdf/benzene.pdf>.

The other document cited in this response (OEHHA, 2000) is available from the same source: (<http://www.oehha.ca.gov/water/phg/pdf/benzene.pdf>).

Comment 8: "In the last paragraph on Page 12 it is unclear what point the author is trying to make in support of enhanced susceptibility of children to benzene. The paragraph indicates that although it is possible to cause chromosomal damage in sperm of rodents, functional effects of this damage have not been observed. The mention of reports of paternal exposure resulting in stillbirths and small birth weight babies are not even "suggestive" as stated in the document without some indication of the degree of paternal exposure and evaluation of confounders and should be deleted."

Response 8: The section is a summary of key reproductive and developmental effects observed in studies of benzene, as previously reviewed by OEHHA (1997). That section of the draft ends with the following summary statement: "These studies, while suggestive, are not definitive and further research is needed." The draft also states that this evidence was

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

reviewed by the Developmental and Reproductive Toxicant Identification Committee of the OEHHA Science Advisory Board, which found that sufficient evidence exists to designate benzene as a developmental toxicant and a male reproductive toxicant under Proposition 65.

Comment 9: "The Maltoni study in Section V.B (Page 13) fails to add anything of value to the question of either induction of childhood leukemia by benzene or enhanced susceptibility of children or the fetus. In the absence of statistical analysis it is impossible to determine the role of chance in the results. This study is plagued with methodological and design flaws. The OEHHA author correctly notes that "It is unclear whether the increased rates are reflective of the increased overall exposure or due to differential susceptibility of the fetus and weanling." In addition, it is unclear whether the increased rates are simply within normal statistical variation or due to other design flaws.

"Since it is generally recognized that there is no animal model of benzene induced leukemia, the relevance of these results (primarily solid tumors) for human risk assessment is minimal. At best, one could say that benzene could act as a transplacental carcinogen in this species – if there had been statistical analysis to account for chance. Even this interpretation is equivocal. Alternatively, it is possible that in utero exposure altered the hematopoietic system of the pup via an epigenetic mechanism which resulted in increased initiation of carcinogenesis during or after lactation.

"Finally, the leukemia data is suspect due to the large gender based disparity between the control incidence data, males – (12/158); females – (1/148). This large gender disparity in control incidence should be verified as normal for this strain of rat. Otherwise, the relevance of the leukemia data in this study are suspect."

Response 9: API's point is well taken; extra caution is warranted when extrapolating across species for different tumor sites that have different patterns of development (e.g., leukemia versus solid tumors). However, the Maltoni *et al.* studies are the only animal cancer studies of benzene that employed exposures prior to weaning. These data provide potentially valuable

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

information with respect to early life carcinogenicity of benzene. OEHHA agrees that lack of a statistical analysis regarding the differences in tumor yield by age at exposure in the Maltoni studies is problematic.

Benzene is a multi-site carcinogen in male and female rats and mice. Increased rates of leukemia are generally not observed among animals exposed to benzene, and increased leukemia rates were not observed among benzene-exposed animals in the Maltoni studies. OEHHA and U.S. EPA carcinogen risk assessment guidelines do not require or expect site concordance across species. However, it is worth noting that cancer potency estimates of benzene derived from occupational studies in humans are very similar to cancer potency estimates derived from animal studies (OEHHA, 2000).

Comment 10: "In the 2nd paragraph of Section V.C.b. several studies that report increased micronuclei in fetal liver cells after in utero exposure to benzene are cited as support for transplacental genotoxicity. While these micronuclei were induced transplacentally, they have no direct relevance to transplacental carcinogenesis. Cells containing micronuclei are not capable of clonal expansion since micronuclei are non-transmissible and lead to cellular death (Preston, 1999)."

"At the top of page 16 in more discussion of micronuclei data and the relative sensitivity of the fetus vs. the dam the author concedes that "...sensitivity relative to dams is unclear." The only studies in which the fetuses appeared to be more sensitive employed i.p. dosing which could result in direct fetal uptake of benzene through the uterine wall as well as via the circulation. This is clearly a route of exposure that has no direct relevance to human exposure."

Response 10: OEHHA agrees that micronuclei have not been associated with carcinogenesis *per se*. Benzene elicits many clastogenic effects in humans, including aneuploidy, ploidy, micronuclei, and chromosomal deletions, translocations and rearrangements (OEHHA, 2000). The micronucleus assay is often used as a marker for clastogenic activity. OEHHA also agrees

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

that the relative formation of micronuclei among benzene-exposed dams and fetuses in these studies is unclear.

Comment 11: "The author states at the end of the 1st paragraph on Page 17 that, "The current unit risk factor for benzene developed under the TAC program does not "specifically" account for the possibility that benzene may induced[sic] childhood leukemia from transplacental or preconceptional exposures." The TAC unit risk factor for benzene has incorporated health conservative assumptions at several points. The upper bound of the slope factor is used rather than the mean. The unit risk factor is based upon all leukemias rather than ANLLs. The assumption of a linear dose-response is made even though the mechanism of leukemia induction is generally agreed to include one or more epigenetic components (Smith, 1996; Irons and Stillman, 1996) and a genetic mechanism involving clastogenesis is necessarily nonlinear due to the requirement for multiple events. The unit risk, also, is calculated from the most health conservative set of exposure estimates from the Pliofilm cohort. For these reasons it is reasonable to assume that the current unit risk factor is sufficiently health protective to adequately protect children or the fetus."

Response 11: Comments noted. However, OEHHA believes that the assumption that clastogenicity equates to non-linearity in all cases is not consistent with available scientific evidence and current thinking about how carcinogenic mechanisms of action in general relate to tumor dose-response relationships (Gaylor, 1992; Hoel and Portier, 1994; Elder and Kopp-Schneider, 1998; Lutz, 1998). In addition, it is still true that the current unit risk factor does not specifically account for potential benzene-induced childhood leukemia following preconceptual or transplacental exposures regardless of the assumptions used in the linear extrapolation model.

Comment 12: "In the last paragraph on Page 17 the author fails to mention that Phase II enzymes involved in detoxification of benzene metabolites also reach adult levels at several months of age which argues against susceptibility based on differences in xenobiotic

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

metabolism young children relative to adults. He also fails to mention that the adult hematopoietic system is continually in a dynamic state of maturation and proliferation which argues against significantly increased susceptibility to benzene-induced leukemogenesis in children. Also, a child's increased exposure per unit air concentration is incorrectly described as "susceptibility". The increased exposure per unit body weight is true, but it is just that, increased exposure, not susceptibility."

Response 12: With respect to differential metabolism, we addressed this in our response to comment 5. OEHHA still contends that a detailed study is needed to predict the metabolism and distribution in the fetus and infant relative to the adult. An important factor that the commenter alluded to is the transfer of maternal-form metabolites to the fetus (Ghantous and Danielsson, 1986), which could be important if detoxification mechanisms such as NQO1 are not operative. Although fetal or neonatal oxygenase activities are underdeveloped, the corresponding Phase II (detoxification) enzyme systems are even less active relative to the adult.

With respect to the comment on the dynamic state of the hematopoietic system, we addressed this in comment 4. Since the hematopoietic system exists in an undeveloped state in the fetal and early postnatal phases, it is necessary that a series of major changes in anatomy, cellular composition, physiology and control mechanisms be achieved during childhood, between the early postnatal period and adulthood. These major architectural and functional changes present a potential window of sensitivity since processes are occurring which are not present in the more stable adult configuration. These changes are quite apart from and in addition to the necessity of growth in cell number in concert with the overall increase in body size during this period.

With respect to reference of increased exposure of children as a susceptibility, the draft will be revised to clarify this point.

Comment 13: "Summary: "In this document OEHHA has attempted to provide support for the position that benzene is a cause of childhood leukemia not only through direct exposure of

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

children but also during gestation and as the result of preconceptional exposure of the parents. Although this review does not address the preconceptional exposure issue a companion review submitted with this one has demonstrated that available epidemiological literature does not support that contention and was selectively reviewed by OEHHA.

"The portion of the OEHHA document, reviewed here, that addresses the potential for increased susceptibility of children to benzene-induced leukemia also suffers from an incomplete review of the available literature and in the area of metabolic differences between children and adults fails to utilize information provided in the generic discussion of childhood susceptibility to environmental toxins in the main report.

"We believe that, although there are clear and substantial differences between the adult and child in some organ systems such as the nervous or reproductive systems, this is not true for the hematopoietic system. The hematopoietic system is relatively unique in that in the adult as in the child there is a continual process of differentiation and maturation of cell types accompanied by an extremely high rate of cellular proliferation. This situation argues against a substantial difference in susceptibility in the child based upon the concept of a developing organ system with rapidly dividing cells.

"We acknowledge that there are differences in xenobiotic metabolism between adults and the fetus and young child. However, as discussed in the main body of the prioritization document many of the enzyme activities involved in the metabolic pathway of benzene reach adult or near adult levels within the first year of life. Therefore, although there is a period of potentially increased susceptibility due to metabolic differences between the adult and child, this period is of relatively short duration.

"In summary, we acknowledge that exposure of the fetus or child to benzene is accompanied by some finite degree of risk of subsequent ANLL. However, we believe that the available information in the peer reviewed literature supports our contention that the degree to which this risk from early exposure is greater than that of adults is adequately accounted for by the

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

inherent health conservatism of the procedure for deriving unit risk factors used by the State of California and the specific data set used for deriving the benzene specific factor."

Response 13: OEHHA thanks API for its careful review of the draft and the well-thought out comments it provided. The Scientific Review Panel will review the comments and responses as part of its deliberations. The proposed TAC listing under SB 25 is subject to change as a result of the public and peer review.

REFERENCES

(References cited in the responses appear in OEHHA's prioritization document)

Crump KS (1994). Risk of benzene-induced leukemia: a sensitivity analysis of the Pliofilm cohort with additional follow-up and new exposure estimates. *J. Toxicol. Environ. Health* 42: 219-242.

Edler L, Kopp-Schneider A (1998). Statistical models for low dose exposure. *Mutat. Res.* 405(2):227-36.

Gale KB, Ford AM, Repp R, *et al.* (1997) Backtracking leukemia to birth: Identification of clonotypic gene fusion sequences in neonatal blood spots. *Proc. Natl. Acad. Sci. USA* 94: 13950-13954.

Gaylor DW (1992). Relationship between the shape of dose-response curves and background tumor rates. *Regul. Toxicol. Pharmacol.* 16(1): 2-9.

Ghantous H, Danielsson BR (1986). Placental transfer and distribution of toluene, xylene and benzene, and their metabolites during gestation in mice. *Biol. Res. Pregnancy Perinatol.* 7(3): 98-105.

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

Hayes RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Travis LB, Li C-Y, Rothman N, Hoover RN, Linet MS, for the Chinese Academy of Preventive Medicine--National Cancer Institute Benzene Study Group. (1997). Benzene and the dose-related incidence of hematologic neoplasms in China. *J. Natl. Cancer Inst.* 89(14): 1065-1071.

Hoel DG, Portier CJ (1994). Nonlinearity of dose-response functions for carcinogenicity. *Environ. Health Perspect.* 102 (Suppl 1): 109-113.

Hommes, GH (1978). The development of DT-diaphorase in rat liver and its induction by benzo(a)pyrene. *Biol. Neonate* 34: 248-252.

Irons RD, Stillman WS (1996). The process of leukemogenesis. *Environ. Health Perspect.* 104(Suppl 6): 1239-1246.

Lee GR, Bithell TC, Foerster F. *et al.* (1993). Granulocytes-Neutrophils. *In* Wintrobe's *Clinical Hematology* (9th Edition) pp. 239-246.

Lutz WK (1998). Dose-response relationships in chemical carcinogenesis: superposition of different mechanisms of action, resulting in linear-nonlinear curves, practical thresholds, J-shapes. *Mutat. Res.* 405(2): 117-124.

Office of Environmental Health Hazard Assessment (OEHHA, 2000) *Public Health Goal for Benzene in Drinking Water*. OEHHA, California Environmental Protection Agency, Oakland, California. Draft, February 2000.

Office of Environmental Health Hazard Assessment (OEHHA, 1997) *Hazard Identification of the Developmental and Reproductive Toxic Effects of Benzene*. OEHHA, California Environmental Protection Agency, Sacramento, California. Draft, September 1997.

Preston RJ (1999). Cytogenetic effects of ethylene oxide, with an emphasis on population monitoring. *Crit. Rev. Toxicol.* 29: 253-282.

Draft Responses to Comments on the March 2001 Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

Ross D, Siegel D, Schattenberg DG, *et al.* (1996). Cell-specific activation and detoxification of benzene metabolites in mouse and human bone marrow: Identification of target cells and a potential role for modulation of apoptosis in benzene toxicity. *Environ. Health Perspect.* 104(Suppl 6): 1177-1182.

Smith MT (1996) The mechanism of benzene-induced leukemia: A hypothesis and speculations on the causes of leukemia. *Environ. Health Perspect.* 104(Suppl 6): 1219-1226.

Smith MT, Fanning EW (1997) Report on the Workshop Entitled: "Modeling Chemically Induced Leukemia – Implications for Benzene Risk Assessment" *Leukemia Research* 21(5): 361-374.

Snyder R, Hedli CC (1996). An overview of benzene metabolism. *Environ. Health Perspect* 104(Suppl 6): 1165-1171.

Snyder R, Kalf GF (1994). A perspective on benzene leukemogenesis. *Crit. Rev. Toxicol.* 24(3) 177-209.

Strobl HM, Takimoto M, Majdic O, *et al.* (1993). Myeloperoxidase expression in CD34+ normal human hematopoietic cells. *Blood* 82: 2069-2078.

Wallin R. (1989). Vitamin K-dependent carboxylation in the developing rat: evidence for a similar mechanism of action of warfarin in fetal and adult livers. *Pediatric Research* 26: 370-376.

Wiemeils JL, Cazzinaga G, Daniotti M, *et al.* (1999) Prenatal origin of acute lymphoblastic leukemia in Children. *Lancet* 354: 1499-1503.