

Comments of Richard A. Becker Ph.D., on behalf of the American Chemistry Council.

Introduction

The American Chemistry Council (ACC or the Council) represents the leading companies engaged in the business of chemistry. ACC appreciates the opportunity to provide comments and perspective on Cal/EPA OEHHA Technical Support Document for Cancer Potency Factors: Methodologies for Derivation, Listing of Available Values, and Adjustments to Allow for Early Life Stage Exposures (23 June 2008) (“CPS Tech Support Document”). Our comments are focused on the issue of early life stage susceptibility to chemical carcinogens and on the proposed application of age specific cancer potency adjustment factors.

Comment 1:

I. The Best Available Scientific Information Needs to be Used in Chemical Risk Assessments

The Council supports the efforts of the government agencies to incorporate advances in scientific methods and practices in health risk assessments. Our members are committed to conducting research and developing safety and health risk data on our products using the best scientific methods available. OEHHA, too, must ensure that the science used is the best available science in its guidance and practice of risk assessment.

The starting point for any risk assessment should be a comprehensive and critical analysis of the available information rather than default assumptions. Consistent with this principle, OEHHA should utilize all available scientific evidence first, before invoking defaults, to provide scientifically-based risk assessments that reflect the best available science. Use of the best available scientific information, including information on biologically plausible modes of action, will provide the public, stakeholders, product stewards and risk managers with high quality risk assessments that reflect the advances in scientific knowledge of the carcinogenic processes gained from extensive biomedical research conducted over the last 30 years. Continued reliance on conservative defaults in cancer risk assessments – defaults developed in the late 1970’s and early 1980’s when much less was known about the molecular mechanisms and biologically process of chemical carcinogenesis – is not consistent with the principle of applying the best available scientific information when conducting risk assessments. Overall, in the CPS Tech Support Document, OEHHA has not demonstrated that there is a sufficiently robust foundation of scientific evidence to justify the Office’s proposal for adding default age-specific cancer slope factor adjustments for estimating theoretical lifetime cancer risks from early life exposures. We believe that a scientifically exacting analysis of the data using a hypothesis-based approach for a weight of evidence evaluation will show that the available data are too limited (both in quantity and quality) to support the OEHHA’s conclusions and OEHHA’s proposal to widely implement a risk assessment policy to apply linear models and age-specific potency adjustments for earlylife exposures to chemical carcinogen risk assessments for all modes of action.

Response:

OEHHA has made it clear at a number of points in the Technical Support Document that where chemical-specific data are available to address a risk assessment decision these are to be used in preference to default assumptions. However, the information on mechanisms and dose response for carcinogenic processes is often partial, even for relatively well-studied chemicals. Use of defaults, which need to be both scientifically informed and public health protective, is therefore often necessary.

There is a fundamental inconsistency in the comment which on the one hand asserts that

“Continued reliance on conservative defaults in cancer risk assessments ... is not consistent with the principle of applying the best available scientific information when conducting risk assessments.”

but then follows by observing that

“OEHHA has not demonstrated that there is a sufficiently robust foundation of scientific evidence to justify the Office’s proposal for adding default age-specific cancer slope factor adjustments for estimating theoretical lifetime cancer risks from early life exposures.”

OEHHA’s conclusion in this specific instance is that there is indeed a lack of robust data to fully inform decisions about differential susceptibility of infants and children to carcinogenesis in every case. A default approach is therefore required to address the legislative mandate to protect the people of California from the effects of “an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health” (California Health and Safety Code, section 39655). We have shown in the document that there are sufficient grounds for suspecting that for many carcinogens exposures during early life stages result in a greater increment in risk than that associated with similar exposures to an adult. We also examine the data available on the magnitude of this increase in risk. Our conclusions are broadly similar to those of the U.S. Environmental Protection Agency (U.S. EPA, 2005), although their analysis (described by Barton et al., 2005) was based on a more limited database than the one we examined in Appendix J of our Technical Support Document. The default policy recommendations we make are consistent with these data, and we believe are adequate to protect public health, but are not particularly “conservative”. The default age adjustment factors are a policy choice informed by science, and are identical to the values chosen as policy by U.S. EPA. Had we for instance chosen to recommend the upper 95% confidence limits on the observed distributions as values of the adjustment factors these would have been significantly higher.

Comment 2:**II. Early Life Exposures and Susceptibility to Chemically Induced Cancer**

When conducting a cancer risk assessment, all relevant data should be used and if there are relevant data for assessing risks from early-life exposures for a particular substance, such data

should be included as part of the overall assessment. With respect to approaches for assessing the contribution of early life exposures to lifetime theoretical cancer risk, there is compelling and robust scientific evidence that mechanisms of carcinogenicity which operate in adults also operate in children, and that to the extent children may be more, less, or equally sensitive to some substances, current cancer assessment methodology is sufficiently conservative to protect children. The Council believes that the current cancer risk assessment methodology is health protective for both adults and children and therefore, application of additional default assumptions and adjustment factors across the board is not warranted. The data actually show that cancer risk from early life exposure can be less than, equal to, or greater than risk from exposures later in life, depending upon the agent and tumor type. Therefore, rather than invoking default cancer adjustment factors for early life exposure across the board, OEHHA should, on a case-by-case basis, examine the scientific database for each chemical to determine whether there are data to indicate increased, decreased or equal susceptibility associated with early life exposure. If such data are available, they should be used in the risk assessment. In the absence of such data, the existing risk assessment methodology, based on averaging daily dose over a lifetime, and health protective assumptions used in extrapolating from animal data to humans and from high to low doses, will protect adults, children and other potentially sensitive subpopulations. The important health-related question is not whether children are more or less sensitive (it is likely that in some cases they will be more sensitive and less sensitive in other cases). The question should be whether children are adequately protected. We believe that the highly conservative methodology currently utilized by OEHHA in its cancer assessments ensures that children are adequately protected.

Response:

OEHHA agrees that chemical-specific data are to be used in preference to defaults when available. We also endorse U.S. EPA's guidance on this point (pages 35-36). In the final paragraph of this section of the TSD (page 41) we state:

“For specific carcinogens where data indicate enhanced sensitivity during age windows other than the immediate postnatal and juvenile periods, or demonstrate sensitivity ratios different from the default ASFs, the chemical-specific data should be used in order to adequately protect public health.”

OEHHA understands that “the Council believes that the current cancer risk assessment methodology is health protective for both adults and children”. However, based on our analysis of the data available, as described in the Technical Support Document and Appendix J, we disagree with this assertion. There is nothing in the current cancer risk assessment methodology that specifically addresses life stage sensitivity. The majority of animal cancer bioassay data does not include exposures prior to sexual maturity. Further, most epidemiological studies of cancer have been in occupationally exposed adults. Thus there is nothing inherent in the studies upon which the potency estimates are based that informs risk estimates for exposures early in life. We also think it important to be able to more accurately inform risk managers of the cancer risks posed by exposing infants and children, as opposed to adults, to carcinogens since this may influence their decisions in practical regulatory situations. This specific consideration of infants and children was mandated by the Children's Environmental Health Protection Act (Senate Bill 25, 1999: Health and Safety Code Sections 39669.5 et seq.).

Comment 3:

Although EPA adopted its Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens in 2005, the Agency specifically states that the cancer potency adjustment factors for early life exposure should only be applied for carcinogens that act through a mutagenic mode of action. Further, EPA states that these default cancer potency adjustment factors would “be used only when no chemical-specific data are available to assess directly cancer susceptibility from early-life exposure to a carcinogen acting through a mutagenic mode of action.” OEHHA should adopt similar guidance for its cancer risk assessment methods, explicitly stating that when data are available, these data trump the default approach.

Response:

As noted in our response to comment 2, we agree that chemical-specific data are to be used in preference to defaults, when available.

As explained further in the Technical Support Document and below (response to comment 4), OEHHA considers that U.S. EPA erred in their recommendation to apply the age-specific cancer potency adjustment factors only for carcinogens that act through a mutagenic mode of action. Their subsequent attempts to define this category have created more confusion than illumination, and a recent draft document on this topic was severely criticized by reviewers.

Comment 4:**III. There is (sic) Insufficient Scientific Data to Support Cancer Potency Adjustment Factors for Nonmutagenic Carcinogens**

With respect to application of cancer potency adjustment factors for early life exposure to carcinogens that act via other modes of action, EPA looked at this issue comprehensively and concluded, unlike OEHHA, that the age dependent adjustment factors for carcinogenic potency should only be applied to chemicals that act to induce cancer via a mutagenic mode of action. EPA reached such a conclusion based on comprehensive analyses of available datasets. EPA concluded, “In the case of nonmutagenic carcinogens, when the mode of action is unknown, the data were judged by EPA to be too limited and the modes of action too diverse to use this as a category for which a general default adjustment factor approach can be applied. In this situation per the Agency’s Guidelines for Carcinogen Risk Assessment, a linear low-dose extrapolation methodology is recommended. It is the Agency’s long-standing science policy position that use of the linear low-dose extrapolation approach (without further adjustment) provides adequate public health conservatism in the absence of chemical-specific data indicating differential earlylife susceptibility or when the mode of action is not mutagenicity.” The available datasets for nonmutagenic carcinogens has not expanded substantially since EPA’s 2005 guidance was issued, and therefore there appears to be a lack of convincing scientific evidence to support OEHHA’s proposal for extending the application of cancer potency adjustment factors for early life exposure to nonmutagenic carcinogens.

Response:

As explained in the Technical Support Document, OEHHA examined not only the evidence assembled by U.S. EPA on this point but also a larger set of data as described in Appendix J. Our conclusion is opposite to that reached by U.S. EPA, namely that the adjustment factors should be applied in all cases except where chemical-specific data indicate the contrary. This conclusion is reinforced by the surprising revelation that several of the carcinogens considered by U.S. EPA in developing their age-specific adjustment factors appear not to qualify as having a primarily mutagenic mode of action according to guidance currently under discussion. The independent analysis by OEHHA, as well as that by U.S. EPA, identified several carcinogens which are generally recognized as having a “non-mutagenic” mode of action (e.g. amitrole, DDT, dieldrin, diphenylhydantoin and polybrominated biphenyls) where increased sensitivity at younger ages was demonstrated. Thus, limiting the adjustment for age-at-exposure to only those chemicals which induce cancer “via a mutagenic mode of action” is not justified as a default position. The U.S. EPA’s Science Advisory Board noted that U.S. EPA needs to work on default adjustments for other carcinogens with other modes of action, including hormonal.

Comment 5:**IV. A Critical Evaluation of the Datasets Underlying the Proposal to Apply Age-Specific Cancer Potency Adjustment Factors Shows that a Substantial Proportion of the Datasets Indicate Decreased Risk from Early Life Exposures, Not Increased Risk**

While the Council has not had an opportunity to fully review OEHHA’s independent evaluation of animal cancer studies which include early life exposures, we have looked extensively at the EPA datasets, which OEHHA relies on to a great extent in proposing adoption of this methodology. EPA’s methods were also reviewed at a 2005 Workshop, the results of which have been published. Using a hypothesis-based weight of evidence approach, Becker (2005) posed the question, “to what extent do the available empirical data which EPA relied on (animal cancer studies which include early life exposures) support the hypothesis that exposure to carcinogens early in life leads to increased probability of tumor development, compared to exposure commencing later in life?”

Response:

In order to evaluate existing data on the effect of age at exposure on carcinogenic potency, we conducted an independent review of a larger dataset in Appendix J, and based our recommendation on that. We are obviously interested in the analysis presented by U.S. EPA (2005) and Barton et al. (2005), and thought it worth presenting in detail in our document since our recommendations largely parallel their findings. The commenter noted that ACC’s comments were presented before they had fully reviewed OEHHA’s analysis. In view of this the criticisms presented of U.S. EPA’s analysis are not strictly applicable to OEHHA’s analysis. However, we have reviewed them for points of interest or relevance. In doing so we were hoping to find a published and peer reviewed document to supplement the brief account given in these comments. However, the reference given as Becker (2005) in the comments is the brief abstract of an oral symposium presentation, which reads, in its entirety, as follows:

“The science behind the development of the guidelines was extensive, but examples of how the guidance would be applied are only beginning to emerge. How might federal and state agencies use the guidance to implement public health or environmental standards? How will the guidance affect decision making for industry?”

It bears noting that U.S. EPA’s Science Advisory Board agreed with the Agency’s analysis of a need to incorporate early life sensitivity to carcinogen exposure when estimating lifetime cancer risk..

Comment 6:

The studies reviewed by EPA that were evaluated by Becker (2005) regarding early life exposures to substances that induce cancer via a mutagenic mode of action consisted of data of 4 chemicals from repeat dose studies, data of 3 chemicals from lifetime exposure studies, and data of 42 chemicals from acute exposure studies. Analysis of the data from the 4 chemicals comprising the repeat dose studies yielded 45 specific datasets (sex, strain, species, and target site) amenable to evaluating the relative potency of early life exposure compared to later life exposure. Of these 45 ratios of susceptibility, 58% showed equal or less sensitivity of the early life exposure period compared to exposure later in life. Analysis of the data from the 3 chemicals comprising the chronic/lifetime exposure studies yielded 6 specific datasets (sex, strain, species, and target site) amenable to evaluating the relative potency of early life exposure compared to later life exposure. Of these 6 ratios of susceptibility, 2 of the 6 showed equal or less sensitivity of the early life exposure period compared to exposure later in life. When these datasets from repeat dose and chronic studies are combined, 55% showed equal or less sensitivity of the early life exposure period compared to exposure later in life (see Figure 1c). Analysis of the data from the 42 chemicals comprising the acute dose studies yielded 515 specific datasets (sex, strain, species, and target site) amenable to evaluating the relative potency of early life exposure compared to later life exposure. Of these 515 ratios of susceptibility, 45% showed equal or less sensitivity of the early life exposure period compared to exposure later in life (see Figure 1d). Is the hypothesis that early life exposure leads to greater susceptibility to cancer supported by the data? Even for substances that act via a mutagenic mode of action to induce cancer, the empirical data indicates the hypothesis is not supported by a substantial proportion of the datasets. Figure 1 graphically illustrates that susceptibility to cancer induction is clearly not always greater for early life exposures, and in fact, extrapolating from the animal datasets, one could reasonably conclude that from 45% to 55% of the time for early life exposure there is actually equal or less susceptibility to cancer induction compared to exposures later in life. This raises the question whether there is sufficient scientific support for applying age specific adjustment factors for early life exposures to carcinogens that act via a mutagenic mode of action, let alone applying such adjustment factors for all chemicals even those where the mode of action is clearly not mutagenicity.

Figure 1. The ratios of juvenile to adult cancer potency for carcinogens acting primarily through a mutagenic mode of action.

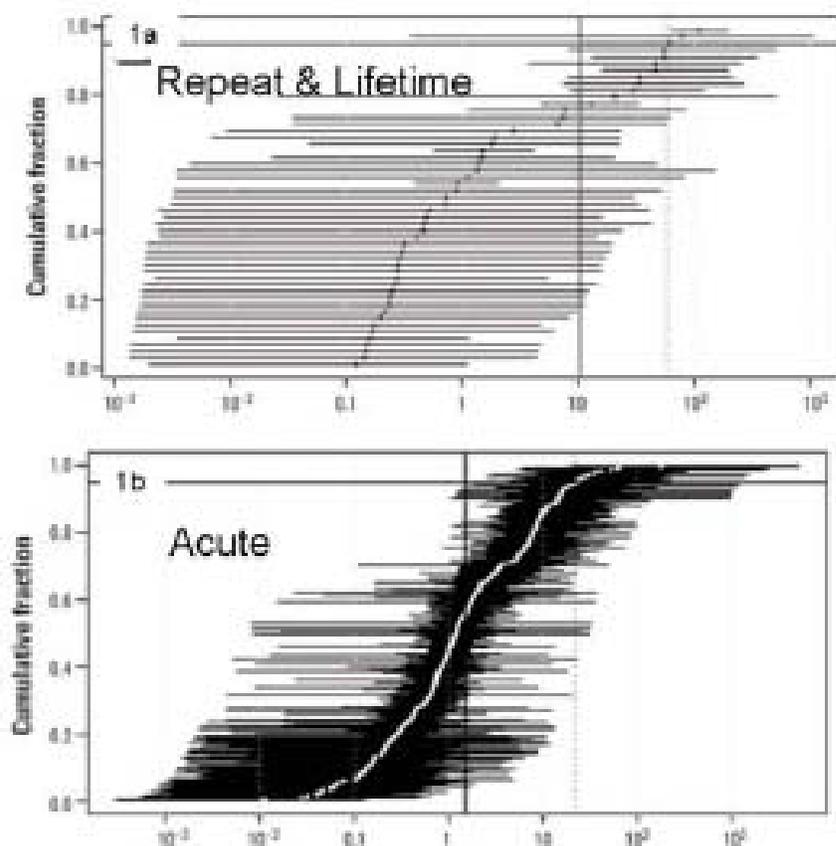


Figure 1a and 1b from Barton *et al.* (2005); 1a depicts the distribution of the ratios for datasets of repeat and lifetime exposure studies and 1b depicts the distribution of ratios of acute exposure studies.

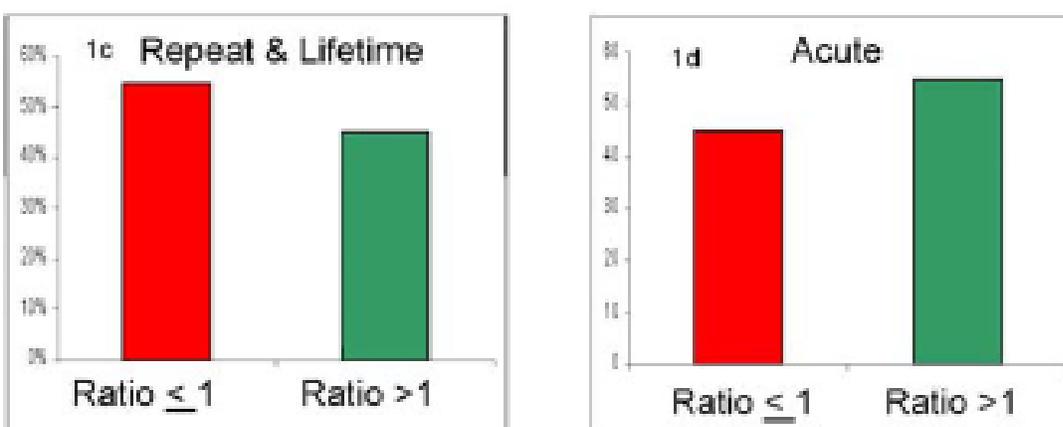


Figure 1c and 1d from Becker (2005); percent of datasets from Barton *et al.* 2005 where the ratios of early life potency to later life potency are below or above unity.

In Barton *et al* Environ Health Perspect. 2005 Sep; 113 (9):1125-33, the description of their Figure 2 is as follows:

“Posterior geometric means and 95% confidence intervals for the ratios of juvenile to adult cancer potency for carcinogens acting primarily through a mutagenic mode of action. (A) Repeated and lifetime exposure studies (geometric mean in black). (B) Acute exposure studies mutagens (geometric mean in white). The horizontal lines to the left and right of each geometric mean correspond to 95% confidence limits. The vertical solid line represents the geometric mean; the horizontal solid line represents the 95th percentile; the vertical dotted line is the geometric mean of the 95th percentile. The geometric mean for repeat and lifetime exposures is 10.4; for acute exposures the geometric mean value is 1.5.”

Figure 1c depicts the datasets of repeat and lifetime exposure studies and 1d depicts the datasets of acute exposure studies. In 1c and 1d, the proportion at or below unity indicates equivalent or lower potency from early life exposures when compared to later life exposures and above unity indicates greater potency from early life exposures when compared to later life exposures.

Response:

As noted in the previous response (Comment 5), ACC’s comments are specific to the U.S. EPA dataset and analysis, and were originally directed to the U.S. EPA, and thus are not directly applicable to OEHHA’s analysis. OEHHA conducted an independent review and analysis of a much larger dataset of animal cancer studies with early life exposure to carcinogens.

Appendix J presents OEHHA’s analyses of multi-window exposure studies conducted in animals. These analyses examined early life susceptibility to carcinogen exposure during three distinct early life stage windows: prenatal (conception to birth), postnatal (birth to weaning), and juvenile (weaning to sexual maturity), and included data from animal studies on 23 unique carcinogens. The purpose of these analyses was to quantify the degree to which early lifestages, as compared to adults, are susceptible to carcinogen exposures, by deriving measures of early-life susceptibility (i.e., age sensitivity factors, or ASFs).

In the analysis of postnatal susceptibility presented in Appendix J, a total of 55 datasets on 18 carcinogens, including two thought to act via primarily non-genotoxic mechanisms, were included. A postnatal age sensitivity factor (ASF) distribution that primarily lies above the value of 1.0 indicates that postnatal exposures to a carcinogen result in a stronger tumor response relative to adult (or, for many cases analyzed here, juvenile) exposures. Conversely, an ASF distribution that mainly lies below the value of 1.0 indicates that postnatal exposure results in a weaker tumor response relative to adult exposure. For two-thirds of the studies plotted – thirty-seven postnatal datasets (for 15 carcinogen)- the ASF distributions are significantly greater than unity (i.e., the lower 95% confidence bound exceeds unity). For sixteen postnatal studies or 29% of the total, representing nine carcinogens, 90% confidence intervals straddle unity. Moreover, for ten of these sixteen postnatal studies (representing all but one of the nine carcinogens), the majority of the ASF distribution lies above 1.0. Two postnatal studies, or only 4% of the plotted studies, representing two carcinogens, have ASF with upper 95% confidence bounds less than unity.

When all the postnatal ASF distributions were combined to derive a single postnatal ASF mixture distribution, depending on the method used to combine the studies, the median unadjusted postnatal ASF value ranged from 4.6 to 7.4, and the mean ranged from 27.1 to 42.4. The increased susceptibility of the postnatal exposure window appears even more pronounced once adjustments are made to take into account the long period cancer has to manifest when exposure occurs early in life. Median estimates of postnatal adjusted ASFs range from 13.4 to 21.6 and mean estimates from 78.5 to 123.1. Thus, the data indicate an inherently greater susceptibility of the postnatal period, as compared to the adult. Moreover, these postnatal ASF estimates may represent underestimates of the true susceptibility of the postnatal period, relative to adults, for some chemicals. This is because many of the studies compared animals exposed during the postnatal age window to animals exposed during the juvenile age window, rather than the adult age window.

Analyses of the prenatal and juvenile datasets presented in Appendix J also demonstrate that these early lifestages can be much more susceptible to carcinogen exposures than the adult lifestage.

With regard to human evidence of early-in-life susceptibility to carcinogens, the scientific literature contains a number of human clinical findings and epidemiological studies of early life cancer susceptibility. Examples include evidence that in utero, but not adult exposures to diethylstilbestrol increase the risk of adenocarcinoma of the vagina and cervix in women (Herbst et al., 1971; Preston-Martin, 1989); exposures in utero and early-in-life to radioactive iodine result in a greater risk of thyroid carcinoma than adult exposures (Moysich et al., 2002); exposures of children under age 18 to immunosuppressive drugs result in a greater risk of post-transplant lymphomas and lymphoproliferative disorders than adult exposures (Penn, 2000); and exposures of girls between the ages of 10-16 to X-irradiation during treatment for Hodgkins lymphoma result in a greater risk of breast cancer than exposures of adults or girls under 10 years of age (Bhatia et al., 1996).

In addition to empirical evidence from humans and animals of in utero and early life susceptibility to carcinogens, there are multiple theoretical bases that suggest that exposures early in life can result in a greater lifetime risk of cancer. These include:

- Cancer is a multistage process and the occurrence of the first stages in childhood increases the chance that the entire process will be completed, and a cancer produced, within an individual's lifetime.*
- Tissues undergoing rapid growth and development may be especially vulnerable to carcinogenic agents. During periods of increased cell proliferation there is rapid turnover of DNA, and more opportunity for misrepair of damage (e.g., DNA breaks, crosslinks, adducts) or epigenetic alterations (e.g., altered DNA methylation, histone modification) to result in permanently altered gene expression that may ultimately lead to cancer.*
- During early development, a greater proportion of the body's cells are relatively undifferentiated stem cells, and as such represent a large target population of somatic cells capable of passing along permanent changes to the DNA during future cell divisions.*

- *There may be greater sensitivity to hormonal carcinogens early in life since the development of many organ systems is under hormonal control (e.g., male and female reproductive systems).*
- *Other factors that may play a role in increased cancer risk from exposures during critical developmental periods include differences in immunological activity, intestinal absorption, biliary and kidney excretion, blood and fat distribution, and expression of enzyme systems that activate or detoxify carcinogens.*

Thus OEHHA concludes that it is appropriate, in the absence of chemical-specific information on early-in-life susceptibility to a given carcinogen, to apply default age-specific adjustment factors greater than unity when estimating cancer risks associated with early life exposures.

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Comment 7:

V. Application of Age-Specific Cancer Potency Adjustment Factors

With respect to the proposal by OEHHA to modify the Office's risk assessment methodology by adding default age-specific cancer slope factor adjustments for estimating theoretical lifetime cancer risks from early life exposures, the Council submits that the datasets to support such a change in approach are limited, and that even for substances that act via a mutagenic mode of action to induce cancer, the empirical data indicates the hypothesis of increased susceptibility from early life exposure is not supported by 45% to 55% of the datasets. Therefore, it appears that there is insufficient scientific support for applying age specific adjustment factors for early life exposures to carcinogens that act via a mutagenic mode of action, let alone all modes of action. The adoption of a policy by OEHHA to apply age specific adjustment factors for early life exposures to carcinogens may have significant impact on regulatory programs in California. Making age-adjustments for both exposure and cancer potency would result in radically new age-specific "annualized" cancer risk estimates. For a given concentration (in air) the amount of

risk accumulated per year from age 0-2 is roughly 30 to 35 fold greater than in any one of the years from age 16-70. The Council submits that adoption of such a change in risk assessment methodology, a change that would have a potentially large impact, should be based on clear and compelling scientific evidence, which appears not to be the case here. Consistent with the provisions of Health and Safety Code 57004, before any board, department, or office within Cal/EPA adopts this approach for use in a regulatory matter, this methodology must be subjected to an independent scientific peer review. Therefore, the Council requests that OEHHA consider all public comments submitted, revise the CPS Tech Support Document accordingly and then conduct an independent scientific peer review in accordance with California Health and Safety Code 57004.

Response:

OEHHA has presented the evidence to substantiate the concern for early life susceptibility to carcinogens. Although the number of chemicals for which such specific data are available is small compared to the total number of identified carcinogens, it is consistent in supporting the proposal of a default approach for use when such compound-specific data are lacking. The impact of the proposed changes is not large, since most regulatory decisions are made on the basis of lifetime risk predictions, and the effect of using the adjustments for age at exposure is to less than double the risk predicted from a steady lifetime exposure.

Any further adjustments relating to breathing rates or other intake rates are not addressed in this document, and will be presented and debated when the revision of the existing Part IV (exposure assessment etc.) technical support document is completed.

OEHHA has already announced in public notices that this document will follow the usual process for Hot Spots guidance. This consists of public comment, to which OEHHA will respond in writing and make any revisions it considers necessary. The revised version will then be presented to the Scientific Review Panel for Toxic Air Contaminants (SRP) for peer review. The comments of the SRP will be taken into account, and any further revisions made before the SRP-approved version of the document is adopted by the Director of OEHHA. It should be noted that review by the SRP satisfies the requirements of Health and Safety Code Section 57004.

Comment 8:

VI. Conclusion

In conclusion, the standard practice of carcinogen risk assessment is already health protective, very conservative and it provides a scientifically plausible upper-bound limit to risk for all age groups. By use of multiple conservative default assumptions in chemical carcinogen risk assessments, regulatory agencies purposely derive quantitative risk estimates that are, by design, unlikely to under estimate actual risks -- the true risks are certainly less and might be as low as zero. Proposals to incorporate additional default adjustments in such cancer risk assessments should be firmly based on a foundation of convincing scientific evidence, not speculation designed to magnify even more the over statement of actual human health risks . Evaluation of the chemical carcinogen datasets which allow direct comparison of risk in lab animals from early life exposures to risk from later life exposures indicates that a considerable number of the

datasets do not support the hypothesis that early life exposure leads to greater risk. In fact, one could reasonably conclude from these datasets that from 45% to 55% of the time there is actually equal or less susceptibility to cancer induction from early life exposure compared to exposures later in life. Therefore, one may reasonably question whether there is a sufficient scientific foundation to support application of age specific cancer potency adjustment factors for early life exposures to carcinogens that act via a mutagenic mode of action, let alone support for applying such adjustment factors for all chemicals, even those where the mode of action is clearly not mutagenicity.

Response:

The standard practice of carcinogen risk assessment involves the analysis of cancer dose response data obtained from cancer epidemiology studies of exposed humans, or, more typically, from cancer studies conducted in animals. In the case of both human and animal cancer studies, study subjects are generally exposed to the carcinogen only as adults (e.g., occupationally exposed human populations; exposure of rodents in two-year bioassays typically begin at six to eight weeks of age – as young adults or older juveniles, depending upon the species and sex). Thus, quantitative estimates of cancer risk are typically based on studies of the effects of adult exposures to a given carcinogen, and do not address the possibility that the fetus, infants, and children may be more susceptible than adults. As discussed in some detail in the response to Comment 6, there are multiple theoretical bases for early life susceptibility to carcinogens, and studies in humans and animals provide empirical evidence of in utero and early life susceptibility. Thus, the assertion in the comment that standard cancer risk assessment practice provides a scientifically plausible upper bound limit to risk for all age groups is incorrect.

The assertion in the comment that animal datasets do not support greater susceptibility of early lifestages to carcinogen exposure is incorrect. As discussed in detail in the response to Comment 6, OEHHA's analyses of multi-window exposure studies conducted in animals indicate that the prenatal, postnatal, and juvenile lifestages can be much more susceptible to developing cancer than the adult lifestage. For example, 47 of the 55 postnatal datasets analyzed in Appendix J, or 85%, indicate a greater susceptibility to cancer induction from postnatal exposure, as compared to adult (or in some cases juvenile) exposure.

Carcinogens often act by multiple mechanisms, and the relative importance of a given mechanism of action may vary with lifestage. OEHHA proposes to apply default cancer potency factor age adjustments to all carcinogens, including those thought to act primarily through non-mutagenic mechanisms, unless data are available which allow the development of chemical-specific age adjustments. As discussed in response to Comment 6, there is human evidence of early-in-life susceptibility to carcinogens thought to act via non-mutagenic mechanisms (e.g., diethylstilbestrol (DES), and immunosuppressive drugs). There is also evidence from studies in animals of early life susceptibility to carcinogens thought to act via non-mutagenic mechanisms, including studies on DES and tamoxifen (summarized in OEHHA, 2001). OEHHA's analyses of multi-window exposure studies conducted in animals include datasets on three chemicals thought to act via primarily non-genotoxic mechanisms, namely DES, DDT, and TCDD. Greater early life susceptibility was observed for DDT and TCDD in these multi-window studies. OEHHA also analyzed data from studies on the non-genotoxic carcinogens diphenylhydantoin and polybrominated biphenyls, in which separate groups of animals were exposed across

multiple “early life” windows (i.e., exposures began prior to conception and continued throughout the prenatal, postnatal and post-weaning periods, up to the age of eight weeks) or during the adult age window. Greater susceptibility was observed for early life exposures to both diphenylhydantoin and polybrominated biphenyls, as compared with adult-only exposures.

In addition to evidence from human and animal studies of early life susceptibility to carcinogens thought to act primarily via either genotoxic or non-genotoxic mechanisms, a large body of evidence from studies of human cancers indicates that epigenetic changes, such as alterations in DNA methylation, are often associated with early events in human carcinogenesis (Baylin, 2005). Common epigenetic changes that arise early in the cancer process have been identified and associated with increased genomic instability and decreased rates of DNA repair (Fraga et al., 2005; Bird, 2007). Recent studies of human glioblastomas, leukemia, and colorectal, pancreatic, and breast cancer have found that each cancer arises as a consequence of both genetic and epigenetic alterations, and that within each cancer type, alterations in any one of several different pathways can result in the cancer (Grady and Carethers, 2008; McLendon et al., 2008; Pedersen-Bjergaard et al., 2008). Thus current understanding of human cancer biology further supports the application of default cancer potency factor age adjustments to all carcinogens.

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Comment 9:

For these reasons, the Council requests that OEHHA review all public comments, then revise the CPS Tech Support Document accordingly and then conduct an independent scientific peer review in accordance with the provisions of California Health and Safety Code section 57004 before applying the proposed age-specific cancer potency adjustment factors in support of any regulatory action in California.

Response:

The statutorily required process for approval of these guidelines for use in the Air Toxics Hot Spots program is already under way. The required consultations with CAPCOA and with interested members of the public have occurred (the latter being the source of this comment letter). Independent scientific peer review is provided for the California Hot Spots and Toxic Air Contaminants programs by the Scientific Review Panel for Toxic Air Contaminants, which satisfies Health and Safety Code Section 57004. A first Panel meeting for discussion of these guidelines, the public comments, and our responses to them has been scheduled.

Comments of Kenneth Bogen of Exponent, Inc

Comment 1:

Paragraph 1 of your June 2008 draft states that using Benchmark dose methods, the multistage cancer risk model fit

"is optimized using likelihood methodology, assuming that the deviations from expected values follow a χ^2 distribution, with the number of degrees of freedom (and hence the maximum number of terms allowed in the polynomial) determined by the number of points in the data set." (page 28)

My understanding is that the BMD method specifies a generic procedure whereby data are fit to a set of data in an observable range using a specified model, "Benchmark risk" (BMR) level, and corresponding Benchmark dose (BMD) level; a lower typically 1-tail 95% confidence limit (95%LCL) on BMD (i.e., BMDL) is calculated as that dose conditional on the model for which the BMR is equal to the corresponding upper limit (95%UCL); and the unadjusted cancer slope factor (CSF) (e.g., pertaining to bioassay animals) is then estimated by linear extrapolation as $CSF = BMR/BMDL$. In the context of your Hot Spots document, the model considered is the multistage (MS) model. However, contrary to your text above, the BMD method per se does not specify how the model should be optimized to the data, nor does it specify how confidence limits should be constructed. Rather,

"The method by which the confidence limit is obtained is typically related to the manner in which the BMD is estimated from the model. When parameters are estimated using the method of maximum-likelihood, confidence intervals (CIs) may be based on the asymptotic distribution of the likelihood ratio or on the asymptotic distribution of the maximum likelihood estimates (MLEs)." [USEPA, 2000 Benchmark Dose Technical Guidance Document, p. 31 - bold added].

Therefore, BMD methodology per se does not preclude fitting the MS model using, e.g., a minimum-chi-square rather than maximum likelihood (ML) optimization criterion, nor does it preclude calculating corresponding confidence limits using bootstrap Monte Carlo methods (e.g., as done by Bogen and Witschi 2002 [attached]). Indeed, a minimum-chi-square optimization criterion would be a more consistent choice if (as is often the case in tumor bioassay data analysis) a chi-square test is used to assess goodness of fit of the model to the data. And bootstrap methods remove unnecessary bias typically introduced by applying approximate, asymptotic ML methods applied to small (e.g., bioassay-sized) samples.

Thus, my comment is that your text should be modified to reflect alternative acceptable model-fitting and confidence-interval-estimation methods, particularly those that yield results that are equally acceptable or superior to those obtained using methods now cited in your text.

REFERENCE: Bogen KT, Witschi HP. Lung tumors in A/J mice exposed to environmental tobacco smoke: estimated potency and implied human risk. *Carcinogenesis* 2002; 23:511-519.

Response:

OEHHA's intention in this section of the document was to identify the specific methods and tools used by OEHHA in its current risk assessment practice, rather than to provide an exhaustive review of the development of these methods and related alternatives. In general, we use either the U.S. EPA's BMDS software, or earlier software such as MStage (Crouch), GLOBAL or ToxRisk (Crump and others). All of these rely on maximum likelihood methods for parameter estimation and construction of associated confidence intervals. However, we are interested in any technical developments in this field, including the several contributions of Dr. Bogen.

The specific quotation given by Dr. Bogen comes from the section describing the "traditional" linearized multistage model which has been used ever since the CDHS (1985) and U.S. EPA (1986) guidelines, not the discussion of benchmark dose methods which actually appears on page 25 of the TSD. All of the standard implementations of the linearized multistage model use maximum likelihood methods. While we note the different approach used by Bogen and Witschi (2002), we have not seen this widely used, nor is packaged software readily available to implement it, so we are unable to recommend it as a default methodology.

While we consider the brief comment on this issue in the TSD to be adequate as a description of our default methodology, we will bear in mind the existence of alternative approaches which may be useful, especially in difficult cases where the standard approach falls short.

Comment 2:

Concerning text that appears on page 29 of the document (paragraph 2 from the bottom):

"Statistical distributions, rather than point estimates, are generated at each site by tracing the profile likelihood of the linear term (q_1) (Zeise et al., 1991). The distributions of q_1 for each of the treatment-related sites are then statistically summed using a Monte Carlo approach and assuming independence. The sum is created by adding the linear term for each tumor site, according to its distribution, through random sampling. The upper 95 percent confidence limit on the summed distribution is taken as the multisite animal cancer potency estimate (McDonald et al., 2003, McDonald and Komulainen, 2005)."

This section cites references to (1) a procedure for calculating complete confidence limits on estimated cancer potency, and (2) the procedure of using an upper confidence bound on the Monte Carlo sum of tumor-site-specific potencies (calculated using procedure #1) to calculate aggregate tumor potency. Earlier references described both procedures in detail and applied both procedures (albeit for procedure 1, using more accurate bootstrap methods rather than a corresponding asymptotic approximation). These earlier references are Bogen & Spear (1987), Bogen (1994), NRC (1994), and Bogen and Witschi (2002). The 1994 paper described & applied both procedures to a large set of heterocyclic amine tumor data.

REFERENCES:

Bogen KT, Spear RC. Integrating uncertainty and inter-individual variability in environmental risk assessment. *Risk Anal* 1987; 7:427-436.

Bogen KT. Cancer potencies of heterocyclic amines found in cooked foods. *Food Chem Toxicol* 1994; 32: 505-515.

National Research Council (NRC). 1994. *Science and Judgment in Risk Assessment*. National Academies Press, Washington, DC, Appendix I.

Bogen KT, Witschi HP. Lung tumors in A/J mice exposed to environmental tobacco smoke: estimated potency and implied human risk. *Carcinogenesis* 2002; 23:511-519.

Response:

Again, OEHHA's intention in this section of the document was to identify the specific methods and tools used by OEHHA in its current risk assessment practice, rather than to provide an exhaustive historical review of the development of these methods and related alternatives. OEHHA acknowledges that there are other examples of the application of this type of approach which have appeared in the scientific literature. The publications provided by Dr. Bogen present methodology that is similar to the methods used by OEHHA; however, the questions and issues addressed in the publications differ from those addressed in the quoted text from OEHHA's document. For example, in Bogen and Witschi (2002), the authors describe an approach to analyze data on tumor multiplicity (i.e., multiple tumors within an animal, all at the same site and of the same type), while the OEHHA document describes the method for generating a multisite potency estimate using data on tumors at multiple sites or of multiple types occurring in the same sex/dose group.

In Bogen and Witschi (2002), the authors note that for the tumor multiplicity studies used in their analyses an assumption regarding the independence of tumors is invoked, stating "such independence is reasonable insofar as each observed tumor was a distinctly separated nodular/neoplastic mass ..." This assumption of tumor independence is also used in OEHHA's analyses with regard to determining a multisite potency distribution, and is consistent with the recommendation of the National Research Council (NRC, 1994) that "In the analysis of animal bioassay data on the occurrence of multiple tumor types, the cancer potencies should be estimated for each relevant tumor type that is related to exposure, and the individual potencies should be summed for those tumors."

Dr. Bogen notes in his comments that the confidence intervals in his references were computed via "accurate bootstrap methods" rather than via a "corresponding asymptotic approximation" method, as has been used by OEHHA. The Wald confidence interval, which is based upon the assumption of asymptotic normality, may lead to lower limits that extend below the value of zero and are clearly unreasonable. This approach is not used by OEHHA, however. Rather, OEHHA uses methodology that employs profile-likelihood methods to compute confidence intervals. Profile-likelihood methods have improved small-sample properties than those based upon asymptotic standard errors calculated from the full likelihood. The asymptotic properties of the profile-likelihood method relate to using the likelihood ratio statistic to determine the

appropriate level of the confidence interval (assumed to have an asymptotically χ^2 distribution with one degree of freedom). For extremely small samples with few tumors, the likelihood function is likely to be quite flat. In this instance, the corresponding interval would be wider than the “true interval,” but would not include implausible values. Conversely, parametric-bootstrapped confidence intervals are unlikely to obtain proper coverage. Furthermore, the computational burden of the profile-likelihood confidence interval is much less than the bootstrapped confidence interval.

The quoted text from page 29 of the document does not, in fact, describe the specific methods utilized by OEHHA in conducting analyses of animal cancer studies with early life exposure, which are presented in Appendix J. The analyses presented in Appendix J involve the computation of potency distributions, while the quoted text describes the derivation of a point estimate of multisite potency. The methodology used to generate a multisite potency distribution is similar to that described in the quoted text, in that profile likelihood methods are employed to trace the likelihood to determine the 0.5% through 99.5% (in increments of 0.5%) confidence bounds of q_1 , the linear slope parameter of the linearized multistage model.

Comments from US Army Center for Health Promotion and Preventive Medicine, Aberdeen Proving Ground, MD.

Comment 1: (D. Bannon)

Several times in the TSD there is mention of the increased susceptibility of children exposed to carcinogens. Though it is important to have in place legislation that protects children, it would be encouraging to see more citations that support the argument of increased risk, particularly in the light of the fact that one of the major risk factors for cancer is increasing age with the related risk of cumulative somatic mutations in adults. There is an argument made in the document that rapidly dividing cells found in embryos/children make them more prone to cancer, but if this were the case, then the children (and embryos) of mothers exposed to toxins (tobacco, alcohol, etc) would have increased cancers, and a quick search in PubMed shows this to be equivocal, with many cross-sectional studies finding no relationship. The annual cancer incidence in adults is about 450 per 100,000 while that of children is about 15 per 100,000 (American Cancer Society) showing a modest non-significant increase in the incidence of all cancers for children from 1992-2004. According to the ACS, 75-80% of all cancers can be attributed to environmental factors, including tobacco use, diet, infectious agents, and occupational exposure. Children are not known to get lung cancers, prostate, breast cancers, or colon cancer, three of the biggest causes of cancer mortality in adults, but leukemia and brain cancers account for 55% of childhood incidence. The question which comes to mind then is this; are childhood leukemia's or brain cancers linked by epidemiology to any environmental cause? The etiology of childhood cancers is elusive but the answer usually involves cancer clusters, which can themselves be highly ambiguous, as noted in this document. If the objective of the proposed age-adjusted default factors in this document is to protect children (i.e. prevent an increase in incidence or reduce the annual incidence) then better evidence of the relationship between environmental exposures and childhood cancers is needed. If, on the other hand, the additional default factors are being introduced as conservative protective factors intended to reduce risk, so that it may be perceived that more is being done to protect children even in the light of weak evidence, then this should be made clear in the document.

Response:

The commenter has misunderstood the basis of OEHHA's proposal to allow for increased potency of carcinogens when exposure occurs early in life. Although the induction of cancers during childhood as a result of exposures to environmental carcinogens is a concern, the age at exposure adjustment factors are meant to apply to lifetime cancer risk. The primary concern on which OEHHA's proposal is based is that early life exposure increases the potency of carcinogens. As is usually the case for exposures to carcinogens, the ultimate appearance of the resulting cancers will generally be many years after the exposure occurred, in adult life or even old age. The estimates of cancer risk discussed in the proposal are for the whole life, not merely the period of infancy or childhood during which the exposures occur.

OEHHA is not arguing that cancer is a major cause of ill-health in children. There are few modern counterparts to Pott's famous documentation of "soot warts" (scrotal cancers)

appearing relatively soon after exposure of young chimney sweeps to the carcinogens in soot. Apart from leukemias, at least some of which appear to have an infectious etiology, other childhood cancers potentially related to early life exposures to environmental agents include lymphoma, brain and testicular cancers (Reis et al. (eds.) (1999). Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995, NIH Publication 99-4649. Bethesda, MD: National Cancer Institute.). However, many cancers appearing in childhood are associated with inherited mutations (where the original mutational event occurred in the parental germ cells, or even in previous generations where the genetic trait responsible is recessive). This issue is further discussed in OEHHA (2001): Prioritization of Toxic Air Contaminants for the Children's Environmental Health Protection Act

Comment 2: (D. Bannon)

The annual incidence of pediatric cancers could be due to sporadic DNA events (i.e. not exposure related) since it has not decreased, even in the presence of dramatic decreases in adult lung cancer related to changes in smoking habits in the US. On the other hand, the most dramatic recent trends in children's diseases seem to be the increases in asthma, diabetes, and autism, at least two of which have the immune system in common. This would seem to highlight the pediatric immune system as a more immediate target of air pollutants, rather the brain (blastomas) or blood system (leukemia).

Response:

As noted in OEHHA's response to the previous comment, the concern is not principally with pediatric cancers, but with pediatric exposures leading to cancer later in life. Nevertheless, OEHHA does not disagree with the premise that immune system responses, especially asthma, are important in children's health. In fact, OEHHA's initial prioritization of TACs for children's health (OEHHA, 2001) and the recently approved Technical Support Document for Determining Noncancer Reference Exposure Levels both presented considerable discussion and analysis of this point.

Comment 3: (L. Tannenbaum)

Page 3, Executive Summary

The page's third paragraph should be rewritten for clarity and to better serve the reader. Please consider using the following rewrite: "The purposes of this document are to provide a summary of ..., to provide the calculation ..., and to describe the procedures ..."

Response:

The document was revised to include the suggested changes.

Comment 4: (L. Tannenbaum)

Page 3, Executive Summary

The first sentence of the page's fourth paragraph should be modified to improve clarity. Please consider the following rewording: "The procedures used to consider the increased susceptibility to carcinogens of infants and children as compared to adults, include the use of age-specific ..."

Also, this paragraph does not mention *in utero* exposures, although the subject document discusses these. On a related note, *in utero* exposures to carcinogens need not necessarily have expression (as tumors) in infants or children (i.e., expression might only/first occur in adulthood). Where appropriate, please endeavor to address this point in the document revision.

Response:

The document was revised to include the suggested wording changes.

The document discusses in utero exposures, but does not include the application of age-specific exposure factors to cancer potency estimates for in utero exposures as a default position. However, the applicability of a cancer potency adjustment factor for in utero exposure will be evaluated on a case-by-case basis, and may be used as evidence develops that supports such use. The document states clearly that the risk estimates calculated are for whole life risks, i.e. risk of cancers appearing at any time including (and most likely occurring in) adulthood.

Comment 5: (T. Tucker)

Page 9, 1st paragraph, last sentence, Selection of Cancer Potency Factor.

The "Technical Support Document for Describing Available Cancer Potency Factors" is referenced. The title of this document is "Technical Support Document for Cancer Potency Factors". Are these the same or different documents? Has the name changed? If the documents are the same, be consistent with the title. If the documents are the same but the title has changed, included a comment informing readers of the change.

Response:

The title description referred to has been changed to "Technical Support Document for Cancer Potency Factors", and a comment noting that the previous versions of this document were entitled "Technical Support Document for Describing Available Cancer Potency Factors" has been added.

Comment 6: (D. Bannon)

Page 10, Cancer Risk Assessment Methodologies

Though there was some discussion of the scientific background related to increased sensitivity in Appendix J (In Utero and Early Life Susceptibility to Carcinogens) three of the four listed children's studies that resulted in increased cancers (page 10) were medical treatments (diethylstilbestrol, X-irradiation for Hodgkin's Lymphoma, immunosuppressive drugs for organ

allograft) while the fourth was the Chernobyl accident. Are there any studies published that establish a link between children's cancer and environmental factors in the context of air pollutants?

Response:

In view of the difficulty in conducting community-based studies that assess children's exposure separately from adults and relate this to lifetime cancer risk, there are few studies which address this question directly, and no air pollution studies of this type were identified. However, the assumption of such increased risks is based on analogy with other agents for which there are human data, as noted here, and the comparability of human cancer induction and similar responses in animals which are subjects of experimental study. In addition to the discussion in the TSD we refer the commenter to the further discussion of this point in OEHHA (2001), the Prioritization of Toxic Air Contaminants for the Children's Environmental Health Protection Act.

Comment 7: (T. Tucker)

Page 10, 3rd paragraph, last sentence, Cancer Risk Assessment Methodologies

The revised document highlights similarities and deviations from the 2005 EPA (Carcinogen Risk Assessment Guidelines) document. While it is acceptable to deviate from EPA's recommendations, the deviations should be identified in a table or appendix. It can be difficult to identify the deviations when they are included only in the text. Recommendation: include the EPA deviations and the rationale for the deviations in a table or as an appendix to the document.

Response:

We quote extensively from U.S. EPA (2005) and Barton et al. (2005) as a useful source of data and prior scientific evaluations. However, there is only one substantial point of difference between OEHHA's recommended procedures and default assumptions and those of U.S. EPA (the intent to apply the age dependent adjustment factors for all carcinogens as opposed to only those with a hypothesized mutagenic mode of action), and so a table seems redundant.

Comment 8: (D. Bannon)

Pages 11-13, Hazard Identification

It has often been cited in pediatrics and environmental studies that "children are not small adults" in that they absorb, metabolize, and excrete toxins in a different way to adults. Is the proposed approach of adding age-specific adjustment factors to already existing adult benchmarks sufficient to treat children as separate to adults? Distinct from adults, should the Hill criteria (and others) as listed on page 11-13 be applied separately to information on cancer in children in order to assess the significance of the hazard to children?

Response:

Hazard identification is seen as an integrative process where hazard to any or all life stages is considered. Data for all life stages are included in the hazard identification process defined, including application of the Bradford Hill criteria. However, as noted in elsewhere (see the responses to comments 1 and 2), the overall evaluation of the impacts of exposures to carcinogens during infancy and childhood is not exclusively about assessing risks of cancers appearing in children, but rather aims to estimate the lifetime cancer risk associated with exposures early in life. The age-specific adjustment factor procedures relate to dose-response assessment rather than hazard identification. Further on in the documentation during the discussion of increased susceptibility of children it is noted that any chemical-specific information on hazard (or dose-response) in utero or to infants or children needs to be considered on its merits: the Bradford Hill criteria are one of several tools which may be applied in evaluating such data.

Comment 9: (T. Tucker)

Page 13, 1st full paragraph, last sentence, Criteria for Causality, Dose-Response

This sentence is not clear. Clarify the point that is being made between active and passive smoking.

Response:

The sentence has been amended to read: “For example, a dose response is observed for various cardiovascular endpoints in the range of exposures characteristic of environmental tobacco smoke, but for some cardiovascular endpoints, the magnitude of the response is little different between active and passive smoking due to saturation of the response at the higher doses associated with active smoking (OEHHA 2005b).”

Comment 10: (T. Tucker)

Page 14, 1st full paragraph, 4th and 5th sentences, Data Sources, Human Studies

The 4th sentence states that the historical database has a bias towards healthy adult males. One could read this to mean healthy adult males of all ethnic groups. However, the 5th sentence states that members of minority ethnic groups hazards analyses may not be accurately characterized, which could include healthy adult males from other ethnic groups. Provide clarity on whether: the healthy adult males in the 4th sentence include healthy adult males for minority ethnic groups and/or if healthy adult males from minority ethnic groups are amongst the population whose hazards are not accurately characterized in the 5th sentence.

Response:

The paragraph in question has been modified to indicate that “The historical database of occupational data has a bias towards healthy white adult males”.

Comment 11: (L. Tannenbaum)

Page 15, Animal Studies

The last sentence of the page's first full paragraph appears to be an understatement. Can the presently worded suggestion that variability is less in inbred lines (compared to wild type) be better substantiated/qualified? Please endeavor to qualify the point being made in the document revision.

Response:

The point being made here appears to be adequately clear if this sentence and the preceding one are read together. The document does not need further explanation that inbreeding would increase genetic homogeneity.

Comment 12: (L. Tannenbaum)

Page 16, Supporting evidence: genetic toxicity, mechanistic studies

A rewording would assist the first sentence of this section's third sentence. Please consider either of the following rewordings: "... mutations in Drosophila ..."; "... mutations in flies (Drosophila) ...".

Response:

The text has been changed to "mutations in flies (Drosophila)".

Comment 13: (L. Tannenbaum)

Page 21, Dose Response Assessment

Comment: In the page's last line, the usual units for cancer slope factors are "(mg/kg-body weight-day)⁻¹". Please consider changing "μg" to "mg".

Response:

The text has been changed to read "(mg/kg-body weight-day)⁻¹".

Comment 14: (L. Tannenbaum)

Page 23, Intraspecies Extrapolation and Inter-individual Variability

Comment: In the third sentence, the phraseology "... that these models do not ..." is incorrect. Recommendation: Please correct the identified phraseology to "that these models are not ..."

Response:

The suggested change is grammatically incorrect. The text in question was re-ordered to improve clarity: "... these models do not explicitly address this type of variability, except in the

few cases where an estimate is based on epidemiological data from a large and unselected study group (U.S. EPA, 2005a)".

Comment 15: (L. Tannenbaum)

Page 30, Early-Lifestage Cancer Potency Adjustments

The third reason given for early (in life) carcinogen exposure resulting in a greater lifetime cancer risk, is not clear/convincing. The text apparently wants to correlate having a large store of undifferentiated (stem) cells, with increased opportunities for cancer to take hold. Is there a basis for this, though? One could argue that there are better opportunities for cancer to take hold only after cells have differentiated, when the differential susceptibilities to cancer of various tissues and organs are realized. The text seemingly is espousing the opinion that the more cells there are of one kind, the greater is the risk factor. Is this true, though? In the document revision, please either substantiate the argument in reason #3, or indicate that the point is conjectural.

Response:

It is a well established principle in cancer biology that once cells are terminally differentiated and lack the capacity for further division, they are much less susceptible to transformation to clones with unlimited cell division potential. (This is for example a key tenet in Moolgavkar's clonal expansion model.) There are many specific instances where more rapidly dividing tissues (i.e. those having more "stem" cells with ongoing division capability) are more susceptible to cancer. The well-known greater frequency of tumor appearance in epithelial tissues is a good example. We have discussed this issue in greater detail in our earlier document "Prioritization of Toxic Air Contaminants for the Children's Environmental Health Protection Act" (OEHHA, 2001). Since the purpose of the Technical Support Document is to summarize the current recommendations for methodology and default assumptions, we decline to elaborate further at this particular point in the document.

Comment 16: (T. Tucker)

Page 33, model equation for PJ, Early-Lifestage Cancer Potency Adjustments

The δ_A should be δ_J for the juvenile period: make the necessary correction.

Response:

The suggested correction was implemented.

Comment 17: (L. Tannenbaum)

Page 35, Early-Lifestage Cancer Potency Adjustments

The page's next-to-last sentence could be modified to improve readability. Please consider rewriting the sentence as: "... and the attainment of a final body height."

Response:

The suggested change was implemented.

Comment 18: (T. Tucker, D. Bannon and L. Tannenbaum)

Page 36, 1st and 2nd full paragraphs, Early-Lifestage Cancer Potency Adjustments

OEHHA proposes applying age-dependent adjustment factors to all carcinogens, whereas EPA recommends doing so only for mutagenic carcinogens. However, paragraph 4 of the Executive Summary, states that age specific factors will not be used at this time. When they are applied, by how much will this change slope factors and unit risk for present carcinogens?

Support for OEHHA's recommended approach is lacking. The subject document correctly identifies an understanding of the toxicokinetics (of a carcinogen) being most relevant to a decision about the appropriateness of applying the adjustment factors, but in this regard, the text has little to offer. It first states (only) a belief: "there is no obvious reason to suppose that the toxicokinetics of non-mutagens would be systematically different from those of mutagens." The text also tries, unsuccessfully we believe, to find the adjustment factors to be applicable for non-mutagenic carcinogens on the basis of a feature that the two types of carcinogens (mostly) share, namely "factors that make individuals exposed to carcinogens during an early lifestage potentially more susceptible than those individuals exposed during adulthood", with some examples being rapid growth and development of target tissues, and greater sensitivity to hormonal carcinogen. We consider that there is insufficient scientific justification for deviation from the EPA's position on non-mutagenic carcinogens.

Non-mutagenic carcinogens are usually promoters i.e. they need a mutational event to come from elsewhere, spontaneous or chemical. Even with non-mutagenic carcinogens (testing negative) there has to be an ultimate mutation (or several) for proliferation and carcinogenesis to take place so non-mutagens could be indirectly mutagenic. It is weakly stated in the paragraph under question "it should be noted that carcinogens that do not cause gene mutations may still be mutagenic by virtue of causing chromosomal damage". Also, one of the things that mutagenic tests do not catch is increased copy number of certain genes that interfere with the cell cycle, such as MDM2. Cancer can also develop out of hyperplasia, (as opposed to neoplasia) when tissue is so badly damaged by a toxin that it grows rapidly to repair itself, increasing the likelihood of a random mutation; this would not be caught by mutagenic testing. It is important also to distinguish between genotoxicity (damage to DNA) and mutagenicity (damage to DNA that is copied, or heritable, during cell division).

Though it is assumed that at this stage that no changes are being made based on the proposed age-dependent adjustments (Executive Summary), it would be helpful if the document would include examples of how the age-adjustments will change known carcinogens so that the changes to current values can be assessed by the end-users, such as the risk assessors. It would be helpful if some examples were provided of how these additional adjustments will impact currently listed cancer slope factors or unit risk values.

Recommendation: Please consider modifying the text here to acknowledge that technically supportive arguments are presently lacking for the application of age-dependent adjustment factors to non-mutagenic carcinogens. Please consider withdrawing the suggested OEHHA policy. If the OEHHA recommendation is to remain, please have the revised text discuss the influence of OEHHA's deviation from EPA's approach on risk assessment outcomes for non-carcinogens. Will under- or overestimates of risk be anticipated?

Response:

The commenters have misread the executive summary: it does not say that the age-dependent adjustments will not be used. It says that the existing cancer potency values (and unit risk values) will not be modified by the procedures in the TSD. In other words, no across-the board factors will be applied to the individual potency values: these will be revised according to the new derivation methods as and when they are considered for updating on a compound-by-compound basis. The age-dependent adjustment factors are applied separately to the risk predicted by existing potency values, depending on the timing and duration of the actual exposure. We expect this procedure to be implemented immediately, and we and CARB are in the process of revising the other technical support documents and supporting software to reflect this. We have prepared some calculated examples showing the effect of the adjustment factors in various situations, and are considering providing these as additions to the document. Examples of similar calculations also appear in the U.S. EPA (2005) supplemental guidance.

We are aware that some analysts have argued for limitation of the adjustment factors to carcinogens with a perceived mode of action which involves mutation as a primary event. We are also aware that efforts to accurately define what this category of carcinogens includes have been controversial and lacking in scientific rigor. We cover the issues in what we consider to be adequate detail in the TSD.

An important factor in our conclusion which is not addressed in this comment is that several compounds clearly identified as “nonmutagenic” by any reasonable criterion show enhanced carcinogenic effects when exposure occurs early in life. Evidence from studies in animals of early life susceptibility to carcinogens thought to act via non-mutagenic mechanisms, including studies on diethylstilbestrol (DES) and tamoxifen was summarized in OEHHA (2001). OEHHA’s analyses in Appendix J of multi-window exposure studies conducted in animals include datasets on three chemicals thought to act via primarily non-genotoxic mechanisms, namely DES, DDT, and TCDD. Greater early life susceptibility was observed for DDT and TCDD in these multi-window studies. OEHHA also analyzed data from studies on the non-genotoxic carcinogens diphenylhydantoin and polybrominated biphenyls, in which separate groups of animals were exposed across multiple “early life” windows (i.e., exposures began prior to conception and continued throughout the prenatal, postnatal and post-weaning periods, up to the age of eight weeks) or during the adult age window. Greater susceptibility was observed for early life exposures to both diphenylhydantoin and polybrominated biphenyls, as compared with adult-only exposures. There is also human evidence of early-in-life susceptibility to carcinogens thought to act via non-mutagenic mechanisms (e.g., DES and immunosuppressive drugs).

Comment 19: (L. Tannenbaum)

Page 36, Early-Lifestage Cancer Potency Adjustments

In the next-to-last sentence of the page's first full paragraph, the word "allows" should appear as "allow". In the fifth sentence of the second full paragraph, "(from conception to birth)" should be "(from post-conception to birth)". Please make the indicated changes.

Response:

The word "allows" was changed to "allow". We decline to change "conception" to "post-conception".

Comment 20: (T. Tucker)

Page 36, 2nd full paragraph, 4th and 5th sentences, Early-Lifestage Cancer Potency Adjustments

The age group definitions used by OEHHA should be identified earlier in the report (page 31), when the age groups are first mentioned. Also, OEHHA deviated from EPA's age group definitions. Recommendations: Provide the age group definitions on page 31. Provide a rationale for deviating from EPA's age group definitions.

Response:

This discussion (both on Page 31 and here) is referring to the age windows used in the analyses of animal studies reported by Barton et al. (2005) and by OEHHA in Appendix J, not the age groups used for application of age-dependent adjustment factors to human risk estimates. OEHHA chose a somewhat different way of subdividing the individual animal studies from that used by Barton et al. (2005) because this was felt to be more appropriate to the different and more extensive data set analyzed by OEHHA. Details of this analysis are to be found in Appendix J.

Comment 21: (L. Tannenbaum)

Page 38, Early-Lifestage Cancer Potency Adjustments

Comment: In the sentence just before Table 2, the word "referent" should probably be "reference".

Response:

"Referent" is correct.

Comment 22: (L. Tannenbaum)

Page 40, Early-Lifestage Cancer Potency Adjustments

Comment: In the fourth sentence of the page's first paragraph, the text is vague when it says "female rats exposed early in the adult period". The text should specify how early this was. Also, the first sentence of the page's second paragraph (i.e., the phraseology of "exposure of a given exposure group ...") should be better written.

Response:

Details of the studies on NMU are provided in Appendix J. The wording of the first sentence of the page's second paragraph was changed to "the period of exposure for a specific exposure group crossed multiple age windows".

Comment 23: (L. Tannenbaum)

Page 41, Other Source Documents for Cancer Risk Assessment Guidance

The word "the" is missing in the first sentence of the section titled "Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986)", after the word "updating".

Response:

The text described above appears to be appropriate, and therefore was not changed.

Comment 24: (T. Tucker)

Page 46, 1st paragraph.

The IRIS potency factors listed in this document were obtained from a 20 year old document (1986 U.S. EPA Guidelines). It would be great to see here guidelines on how the cancer potency values could be updated using the latest guidance, such as a reassessment of a chemical or new chemical. Provide justifications for when the latest guidance could be used for chemicals.

Response:

Response: The IRIS potency factors are not all from 1986, but date from various years up to the present. The basic methodology, however, was published in 1986, and updated along the way including formally in 2005.

The implementation of age-dependent adjustment factors (AAF) or other methodological changes described in this document will not be used to impose any overall revisions of the existing cancer potencies and unit risks. Individual chemicals will be reassessed over time. OEHHA has no mechanism for automatically adopting updates from U.S. EPA. Any such updates would need to be run through the same public and peer review processes as other revisions.

Comment 25: (L. Tannenbaum)

Page 46, OEHHA Calculation of Carcinogenic Potency Based on Animal Data

This section's first sentence is unnecessarily wordy. Please rewrite the sentence as: "... in a cell is transmitted to successive cell generations."

Response:

The sentence in question was modified from "cell descendents from that cell," to "cell descendents,".

Comment 26: (L. Tannenbaum)

Page 47, OEHHA Calculation of Carcinogenic Potency Based on Animal Data

The fourth sentence of the page's first full paragraph is not understood when it says "... the malignant tumors are significantly increased". Is the text there referring to an increase in size of malignant tumors, or perhaps, the malignant tumors being greater in number than the benign tumors that are mentioned earlier in the sentence? In the document revision, please clarify the wording of the indicated sentence for the reader.

Response:

This sentence has been edited to improve readability. The original text read "Where both benign and malignant tumors are induced at the same site and the malignant tumors are significantly increased, the data on both types of tumors could be combined to form the basis for risk assessment". The edited text reads "Where both benign and malignant tumors are induced at the same site and the benign tumors are considered to have the potential to progress to malignant tumors, the incidence data for both types of tumors could be combined to form the basis for risk assessment".

Comment 27: (L. Tannenbaum)

Page 49, Expedited Proposition 65 Cancer Risk Assessment Methodology

Comment: Assumption #5 mentions "cancer hazard". What is this? Also, it would be prudent here to briefly elaborate (with either text or a simple numerical example) what is meant by "cancer hazard increasing with the third power of age". Please have the text define the term "cancer hazard", and please refer the reader to page 51 where there is discussion and an equation on the subject of increasing development of cancer with age.

Response:

The term "cancer hazard" has been changed to "cancer risk". The information that age-specific incidence continues to increase as a power function (e.g., t^3 or t^4) of the elapsed time since initial exposure was provided prior to the Expedited Proposition 65 Cancer Risk Assessment Methodology description on page 49.

Comment 28: (L. Tannenbaum)

Page 50, Expedited Proposition 65 Cancer Risk Assessment Methodology

Condition #3 should be qualified; seemingly the only route of administration that is not recognized is dermal contact (topical application). Condition #5 should be qualified, with a definition of "chronic", and with specification regarding the scheduling of exposures. Please consider rewording Condition #3 as: "Routes of administration are other than topical application". In Condition #5, please define "chronic exposure" (probably in terms of percentage of a lifespan), and please insert the words "any two" after the word "between" in the latter part of the Condition.

Response:

Response: Condition #3 exactly specifies which routes of exposure were included in the study evaluations, and were taken verbatim from Gold et al., 1984. It is unclear what benefit would be gained from the suggested rewording. Condition #5 has been edited to include the definition of "chronic" used in the generation of the Carcinogenic Potency Database by Gold et al. (1984): "duration of exposure was at least one-fourth the standard lifespan for that species".

Comment 29: (L. Tannenbaum)

Pages 50 to 51, Expedited Proposition 65 Cancer Risk Assessment Methodology

Notwithstanding selection criterion #4 (page 51), one would think that an additional selection criterion for dose response data would be preference for a two or dual sex study. Please consider adding this suggested criterion.

Response:

This document did not generate the Expedited Proposition 65 Cancer Risk Assessment Methodology de novo. Rather, it describes the methodology developed for the Proposition 65 program used to develop expedited Proposition 65 cancer potency values from the Carcinogenic Potency Database which have been adopted for use by the Hot Spots program. This document is not the appropriate venue for changing the Expedited Proposition 65 Cancer Risk Assessment Methodology.

Comment 30: (L. Tannenbaum)

Page 51, Expedited Proposition 65 Cancer Risk Assessment Methodology

Regarding the discussion of the page's next-to-last paragraph, is there a minimum exposure duration for a study to be deemed appropriate for use? If so, what is the minimum duration; if not, why? Would an 'adjustment' such as is described here for a particularly short experimental duration, accomplish anything? Also, "Excess mortality" is mentioned at the start of the page's last paragraph, but the term is not qualified. Should a study with an associated excess mortality be used in cancer risk assessments altogether? Why?

Response:

- 1) *As addressed above in the response to Comment #29, the minimum exposure duration for studies evaluated using Expedited Proposition 65 Cancer Risk Assessment Methodology was one-fourth the standard lifespan for the study species.*
- 2) *Lifetime chemical exposure and observation are preferable in any cancer bioassay, but useful tumor data can be obtained from less-than-lifetime exposure experiments. The exposure duration adjustment used in the Expedited Proposition 65 Cancer Risk Assessment Methodology was used to improve the accuracy of the potency calculations.*
- 3) *As taken in the context of this document section, "Excess mortality" would mean poor subject animal survival as noted by Gold et al.; if sufficient time-to-tumor data is*

available, then a cancer bioassay demonstrating excess mortality may still be useful in generating a cancer potency value.

Comment 31: (D. Bannon)

In Appendix A (Hot Spots Unit Risk and Cancer Potency Values) one of several different sources can be cited for a listed unit risk or slope factor. When several sources (IRIS, OEHAA, etc) make different numbers available, what criteria are used to select one of these sources over the other?

Response:

The slope factor or unit risk listed is the one which has been adopted for use in the Air Toxics Hot Spots program. In general, the order of preference is for numbers developed by: OEHHA air programs (Hot Spots and Toxic Air Contaminants), other OEHHA programs (drinking water, Proposition 65, school sites etc.), IRIS, other U.S. EPA programs, other sources. In each case the individual number is reviewed and adopted specifically by the Hot Spots program: there is no automatic adoption or update process.

Comment 32: (T. Tucker)

In Appendix K, some of the corrections are self explanatory (correct CAS number), however some are not. Include the rationale for additions and corrections, such as reassessed under 2005 guidance, new chemical or incorrect value used for a parameter.

Response:

The additions and corrections listings seem to be sufficiently self-explanatory.

Comments from Michael D. Wang on behalf of the Western States Petroleum Association.

Comment 1:

Comment: WSPA is encouraged by OEHHA 's agreement that any revisions to existing risk based levels would "require the originating program to reconsider the value in an open public process." The open process is important in light of perhaps WSPA's greatest concern - the proposal for age sensitivity factors (ASFs) which OEHHA has developed to account for differences in susceptibility for in utero and early life exposures to carcinogens. As noted in the document, these ASFs can raise risk estimates 50-70% and could have broad application if used in health risk assessments conducted for several programs administered by CalEPA. For these reasons, WSPA believes that the TSD deserves careful and thorough consideration and review by the Scientific Review Panel.

Response:

OEHHA's remark on revisions of course relates to potency factors etc. determined by OEHHA, not "risk based levels" if the latter is interpreted to mean control levels determined by a risk management authority. CARB, air districts and other risk managers have open processes for setting and modifying their regulatory actions.

We believe that the Technical Support Document (TSD) for Cancer Potency Factors will receive the same careful and thorough consideration and review by the Scientific Review Panel (SRP) that other documents have received in the past.

Comment 2:

Comment: WSPA has several comments specific to the proposed ASFs. While we are pleased that OEHHA is attempting to be consistent with U.S. EPA in selecting default ASFs (consistent with the 2005 US EPA Supplemental Guidance), we suggest the TSD include a table listing the default ASFs to avoid confusion with the numerous ASFs presented in the main text and Appendix J.

Response:

The values proposed are listed on P. 35-36 of the TSD. However, it appears from this and other comments received that a table would improve clarity, so this has been added.

Comment 3:

It should be noted that the U.S. EPA chose to address the issue of age sensitivity to carcinogens in a Supplemental Guidance document that, according to the Preface is intended as "guidance only" and "has no binding effect on EPA or any regulated entity."

We cite the following from the EPA Supplemental Guidance document,

“Therefore, the Supplemental Guidance has no binding effect on EPA or on any regulated entity. Where EPA does use the approaches in the Supplemental Guidance in developing risk assessments, it will be because EPA has decided in the context of that risk assessment that the approaches from the Supplemental Guidance are suitable and appropriate. This judgment will be tested through peer review, and the risk assessment will be modified to use different approaches if appropriate.

This Supplemental Guidance is intended for guidance only. It does not establish any substantive “rules” under the Administrative Procedure Act or any other law and has no binding effect on EPA or any regulated entity, but instead represents a non-binding statement of policy.”

(Preface, page vii, "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens," USEPA, 2005.

Given the underlying uncertainty of the proposed ASFs and the USEPA's view that they should be treated as guidance, WSPA believes that ASFs should be used only with great caution and not set hard-fast rules for conducting health risk assessments under CalEPA programs. Furthermore, WSPA believes that until the underlying mechanisms of age specific sensitivity are better understood and the large uncertainties addressed, that the TSD should discourage local regulatory bodies from using ASFs for determining "bright line" risk based regulatory values.

Response:

Nothing in the language describing the U.S. Environmental Protection Agency's supplemental guidance document (U.S. EPA, 2005) prevents OEHHA from adopting principles identified in that document in the TSD. Our conclusions are broadly similar to those of the U.S. EPA (2005), although their analysis (described by Barton et al., 2005) was based on a more limited database than the one we examined in Appendix J of our TSD. We refer to the U.S. EPA's guidance documents because we use data they have compiled, and agree with many, although not all, of their conclusions, not because we rely on any authority of U.S. risk assessment programs over California's activities in this area.

The U.S. EPA's guidance documents are designed to lay out general principles and defaults which will be used, subject to the specific data available and the judgment of the analyst preparing an individual risk assessment. In any assessment the guidance will be followed in ways that are appropriate to the specific case, which will involve departure from defaults where indicated by specific data. OEHHA will also evaluate data specific to a given chemical and use judgment in applying the ASFs. However, the analyst is not expected to depart from the guidelines capriciously or without clearly stated justification.

It should be noted that the TSD also states that alternative ASFs may be used when data are available which allow for the development of chemical-specific cancer potency factor age adjustments. In those cases, an agent-specific model of age dependence (based on observational or experimental data) might be used, or alternative (larger or smaller) adjustment factors and age ranges may be applied where understanding of the mechanism of action and target tissues makes this appropriate.

OEHHA believes that the data concerning early-life susceptibility to carcinogens collected and evaluated by U.S. EPA and OEHHA indicate that the development and use of ASFs in cancer risk assessment is necessary for public health protection. Risk managers such as CARB and the Air Quality Management Districts have the discretion, and the sole authority, to determine how risk assessments prepared according the Hot Spots guidelines are translated into actual regulatory actions.

Comment 4:

One clear distinction between the OEHHA TSD and the USEPA Supplemental Guidance is that OEHHA would apply the ASFs to all carcinogens while the USEPA restricts their application to genotoxic carcinogens. WSPA believes that the OEHHA TSD should be consistent with the USEPA Supplemental Guidance. The need for greater consistency between CalEPA and USEPA risk assessment guidance was one of the conclusions of the Risk Assessment Advisory Committee (October 1996). WSPA concurs with this conclusion and recommends that the OEHHA TSD restrict the application of ASFs to genotoxic carcinogens.

Response:

OEHHA has examined the evidence, as described in the TSD, and reaches a different conclusion from that presented by U.S. EPA with regard to the application of age-specific adjustment factors to various classes of carcinogens.

Carcinogens often act by multiple mechanisms, and the relative importance of a given mechanism of action may vary with lifestage. OEHHA proposes to apply default cancer potency factor age adjustments to all carcinogens, including those thought to act primarily through non-mutagenic mechanisms, unless data are available which allow the development of chemical-specific age adjustments. There is human evidence of early-in-life susceptibility to carcinogens thought to act via non-mutagenic mechanisms (e.g., diethylstilbestrol (DES), and immunosuppressive drugs). There is also evidence from studies in animals of early life susceptibility to carcinogens thought to act via non-mutagenic mechanisms, including studies on DES and tamoxifen (summarized in OEHHA, 2001: Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act).

OEHHA's analyses of multi-window exposure studies conducted in animals include datasets on three chemicals thought to act via primarily non-genotoxic mechanisms, namely DES, DDT, and TCDD. Greater early life susceptibility was observed for DDT and TCDD in these multi-window studies. OEHHA also analyzed data from studies on the non-genotoxic carcinogens diphenylhydantoin and polybrominated biphenyls, in which separate groups of animals were exposed across multiple "early life" windows (i.e., exposures began prior to conception and continued throughout the prenatal, postnatal and post-weaning periods, up to the age of eight weeks) or during the adult age window. Greater susceptibility was observed for early life exposures to both diphenylhydantoin and polybrominated biphenyls, as compared with adult-only exposures.

We recognize the desirability of retaining comparability in general with U.S. EPA risk assessment practice, and in fact the values of the age adjustment factors that OEHHA proposes

are the same as those adopted by U.S. EPA. However, this aim for comparability does not override the clearly stated requirement to use the best scientific evidence, and the expert judgment of the State's staff scientists and peer reviewers, to protect public health.