FINAL STATEMENT OF REASONS
TITLE 27 CALIFORNIA CODE OF REGULATIONS

SECTION 25705(b). SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

This is the Final Statement of Reasons for a specific regulatory level for ethylbenzene**,** a chemical listed as known to the State to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986 (hereinafter "the Act" or Proposition 65; Health and Safety Code, section 25249.5 *et seq*.). On March 28, 2008, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt the proposed regulatory level for ethylbenzene for adoption in Title 27, California Code of Regulations, section 25705(b)[1]. The Initial Statement of Reasons set forth the grounds for the proposed regulations. A public comment period was provided from publication of the Notice until May 12, 2008. The Notice of Proposed Rulemaking stated that a public hearing would be held only on request. No request for a public hearing was received by OEHHA.

On March 28, 2008, OEHHA provided the technical support document forming the basis for the proposed regulatory level for ethylbenzene to the members of the Carcinogen Identification Committee for their review and comment as required by Section 25302(e). No comments were received from any committee members.

On February 10, 2009, a notice was filed to add six references to the rulemaking file for ethylbenzene. No comments were received by February 26, 2009, the end of the 15-day comment period.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED

One set of comments was received from Sharon H. Kneiss on behalf of the American Chemistry Council regarding the No Significant Risk Level (NSRL) for ethylbenzene.

Comment:
Sharon H. Kneiss commented that "In the TAC [Toxic Air Contaminant] Risk Assessment for ethylbenzene, OEHHA failed to give appropriate weight to the consensus findings by the distinguished scientists on the VCCEP [Voluntary Children's Chemical Evaluation Program] Panel."

Response:
OEHHA is aware of the consensus findings of the VCCEP Panel related to modes of action (MOAs) for kidney tumors in rats and liver and lung tumors in mice exposed to ethylbenzene. OEHHA previously considered the opinions of the VCCEP Panel and

[1] All further section references are to Title 27 of the California Code of Regulations, unless otherwise noted. Note that the Proposition 65 regulations formerly located in Title 22 have been moved to Title 27 and renumbered.

concluded that there is not enough evidence to accept the VCCEP Panel's conclusions on the MOAs (OEHHA, 2007a). OEHHA considered all relevant data on MOAs for ethylbenzene and stands by its previous scientific conclusions (OEHHA, 2007a; 2007b). An expert panel of external scientists (the Scientific Review Panel [SRP] on Toxic Air Contaminants) reviewed, deliberated on, and approved OEHHA's (2007b) risk assessment and response to public comments (OEHHA, 2007a).

Comment:
Sharon H. Kneiss commented that "the TAC Risk Assessment also is based on an unprecedented and unreasonable standard for acceptance of scientific evidence establishing a mode of action (MOA)," and questions OEHHA's use of the phrase, "reasonable scientific certainty." Further, she commented that OEHHA did not follow US EPA's 2005 Guidelines for Carcinogen Risk Assessment and asserts that OEHHA's approach to evaluating an MOA is "arbitrary and inflexible."

Response:
OEHHA (2007a; 2007b) considered the MOAs for all three tumor types in the ethylbenzene risk assessment and the commenter's points on each MOA are addressed in subsequent responses below. OEHHA concluded that "the limited data do not conclusively establish any particular MOA for ethylbenzene carcinogenesis. However, one or more genotoxic processes appear at least plausible and may well contribute to the overall process of tumor induction." (OEHHA, 2007b) OEHHA's approach to the MOA evaluation was clearly stated, supported by scientific evidence, put out for public comment, and subject to scientific peer review by the SRP. The SRP evaluated OEHHA's scientific conclusions on the MOAs for ethylbenzene and approved the risk assessment.

OEHHA's (2007a) use of the phrase, "reasonable scientific certainty" was in response to a commenter's (the Western States Petroleum Association) assertion that the "most likely" MOA should be used. OEHHA disagreed with this assertion, responding that an MOA "should be established with reasonable scientific certainty, as opposed to being hypothesized" (OEHHA, 2007a). The scientific evidence was evaluated by OEHHA for each potentially relevant MOA.

Although OEHHA is not bound to the U.S. EPA cancer guidelines (OEHHA, 2007a), OEHHA used similar methods (*e.g.*, Hill criteria) as U.S. EPA in evaluating the MOAs proposed by the commenter. As noted above, the SRP reviewed and agreed with OEHHA's (2007b) scientific conclusions in the ethylbenzene risk assessment.

Comment:
Sharon H. Kneiss commented that "the NSRL process affords OEHHA the discretion to utilize alternative MOAs for a substance like ethylbenzene where the scientific evidence is compelling."

Response:
All relevant, well established alternative MOAs are considered under the NSRL process and were considered for ethylbenzene. The reasons for not applying the particular MOAs

discussed by the VCCEP Panel have been previously discussed by OEHHA (2007a; 2007b) as outlined below. OEHHA concluded that the limited data do not conclusively establish any particular MOA for ethylbenzene carcinogenesis (OEHHA, 2007b). This conclusion was reviewed by the SRP who agreed with the assessment.

Comment:
Sharon H. Kneiss asserts that OEHHA should "correctly apply the modified Hill criteria and adopt the same alternative MOAs accepted by the VCCEP Panel."

Response:
OEHHA (2007a) already extensively addressed this comment and incorporates that discussion by reference here. OEHHA reviewed the VCCEP Panel's alternative MOAs, including a consideration of the modified Hill criteria. OEHHA disagrees with the VCCEP Panel's conclusions on MOAs as described in detail in OEHHA (2007a; 2007b) and reaffirmed in this Final Statement of Reasons.

Comment:
Sharon H. Kneiss commented that OEHHA should "base its risk assessment on those tumors in animals that were induced by a mechanism most likely to be relevant to humans." The commenter goes on to say that "OEHHA's characterization of the Panel's position is not correct in that the assumption of nonconcordance must include consideration of the nature of the proposed MOA."

Response
OEHHA based the dose-response assessment on the most sensitive, most appropriate tumor site, which was the male rat kidney. The limited data do not establish any particular MOA for ethylbenzene carcinogenesis for any of the target sites in the species and sexes tested (OEHHA, 2007b). OEHHA's dose-response assessment was reviewed by the SRP and is consistent with Proposition 65 regulations for derivation of cancer potency (Section 25703).

Comment:
Sharon H. Kneiss commented that "the genotoxic MOA for ethylbenzene is not supported by the applicable scientific evidence and the OEHHA risk assessment should not use a quantitative model that implicitly assumes genotoxicity." The commenter asserts that the OEHHA TAC document did not consider the genotoxicity testing reported in Henderson et al. (2007) and disagrees with OEHHA's interpretation of Midorikawa et al, (2004).

Response
OEHHA has reviewed all the genotoxicity studies and proposed a plausible genotoxic mechanism involving DNA damage as a result of the formation of quinone metabolites (OEHHA, 2007b). The paper by Henderson *et al.* (2007) is a review of existing genotoxicity studies on ethylbenzene that were already reviewed by OEHHA (2007a; 2007b). There are no data in Henderson *et al*. (2007) relevant to ethylbenzene's genotoxicity that was not already considered by OEHHA.

OEHHA (2007b) concluded that one or more genotoxic processes appear at least plausible and may well contribute to the overall process of tumor induction. In addition to genotoxicity, there are several other diverse MOAs through which chemicals can cause cancer, ranging from epigenetic effects on gene expression, to altered cell signaling, to immune response modulation. Carcinogens can and frequently do act through multiple MOAs. The MOAs through which ethylbenzene acts have not been well studied, although observations of genotoxic metabolites suggest that a genotoxic MOA is involved.

OEHHA (2007a) explained that we have not claimed a genotoxic MOA for ethylbenzene but also have not concluded that genotoxicity plays no role in ethylbenzene-induced cancer. OEHHA (2007a) noted that the observation of oxidative DNA damage *in vitro* (Midorikawa *et al*., 2004) raises some interesting questions about downstream metabolites, including the analogy with benzene (a well-known genotoxic carcinogen targeting multiple sites in various species including humans). More recently Chen *et al*. (2008) reported positive results for ethylbenzene in the comet assay, showing the induction of single DNA strand breaks. This new study provides strong support for the genotoxicity of ethylbenzene.

There simply are not sufficient data at present to make a definitive conclusion regarding the MOA for ethylbenzene carcinogenesis, or to rule out genotoxic activity. No convincing MOA has been established for key tumor endpoints, even in systems *in vitro*, that would support an alternative approach to the quantitative dose-response assessment. There are insufficient data to conclusively determine the MOA for ethylbenzene carcinogenesis.

Comment:
Sharon H. Kneiss commented that "the kidney tumors in rats were clearly attributable to CPN [chronic progressive nephropathy], a mechanism which has no relevance to humans." She also states that the papers by Lock and Hard (2004) and Wolf and Mann (2005) were not reviewed in the TAC Risk Assessment.

Response
OEHHA (2007b) considered the proposed CPN mechanism for kidney tumors induced by ethylbenzene in rats and found no basis to support a conclusion that the sole or primary cause of the kidney tumors is exacerbation of CPN. OEHHA (2007a) concluded that the Hill criteria have not been sufficiently satisfied for this mechanism.

Wolf and Mann (2005) is an examination of confounders in the interpretation of pathology results for risk assessment. This paper includes a discussion of the CPN mechanism in general, with ethylbenzene cited as an example. However, Wolf and Mann (2005) provide no new data to support the CPN mechanism for ethylbenzene. Similarly, the Lock and Hard (2004) review paper provides no new data on ethylbenzene relevant to the CPN mechanism. OEHHA thoroughly reviewed the Hard (2002) CPN hypothesis and found that this proposed mechanism was not sufficiently supported by the available data. The SRP reviewed and agreed with OEHHA's opinion.

Comment:
Sharon H. Kneiss commented that "the liver tumors in female mice were clearly associated with hepatic enzyme induction, and this mechanism also has no relevance to humans."

Response:
OEHHA (2007a; 2007b) considered the hepatic enzyme induction MOA for liver tumors in female mice and disagrees with the conclusions of the VCCEP Panel. As discussed previously (OEHHA, 2007b), the data from which a correlation between liver eosinophilic foci and liver tumors was inferred are not consistent or convincing and OEHHA stands by the scientific conclusion that a correlation does not indicate a causal relationship. OEHHA (2007a) concluded that the very limited data do not establish a lack of any genotoxic MOA for the liver cancer endpoint.

Comment:
Sharon H. Kneiss commented that "the lung tumors in male mice are the only animal tumors that may be relevant to humans, and it is clear that these tumors were caused by a nonlinear MOA… Moreover, since the proposed MOA for these tumors is a threshold mechanism, OEHHA should calculate a reference concentration using an MOE [margin of exposure] from the no effect level for cytotoxicity rather than utilizing a linear dose-response model."

Response:
OEHHA previously considered the VCCEP Panel's proposed non-linear MOA for lung tumors in male mice. OEHHA (2007a; 2007b) discussed the plausibility of quinone metabolites participating in a potential MOA for ethylbenzene-induced lung cancer in mice. OEHHA found the suggestion that the role of these metabolites is confined to cytotoxicity (resulting in promotion of spontaneous tumors) not convincing. Since ring oxidation may produce a genotoxic epoxide metabolite, it is possible that more than one MOA may be operating. The SRP reviewed this finding and agreed with it.

OEHHA has concluded that there is insufficient evidence to determine the MOAs for the other tumor sites and therefore does not agree that the lung tumors are the only animal tumors that may be relevant to humans. In addition, tumor site concordance between experimental animals and humans cannot be assumed, and is seldom observed even between rodent species. The commenter's assertion that the lung is the only relevant tumor site is not supported by the available data for ethylbenzene.

Regarding the dose-response for lung tumors, the plausibility of involvement of quinone metabolites does not in itself establish the quantitative nature of the dose-response relationship. It is very plausible that a mechanism involving oxidative DNA damage might display low-dose linearity (OEHHA, 2007a). In addition, if another MOA were also operating, assessing the dose-response relationship under that MOA would not merely involve applying uncertainty factors to derive a reference concentration as a substitute for a cancer potency.

ALTERNATIVES DETERMINATION

In accordance with Government Code section 11346.5(a)(7), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more effective in carrying out the purpose for which the regulations were proposed, or would be as effective and less burdensome to affected private persons than the proposed action. OEHHA has determined that no alternative considered would be more effective, or as effective and less burdensome to affected persons, than the proposed regulation.

For chemicals listed under the Act as known to cause cancer, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure poses "no significant risk" of cancer (Health and Safety Code, section 25249.10(c)). The Act does not specify numerical levels of exposure that represent no significant risk of cancer.

The purpose of this regulation is to provide a "safe harbor" level for a particular chemical exposure. This regulation establishes the numerical no significant risk level for one carcinogen, ethylbenzene. At or below this level, the Act does not require a warning regarding cancer or prohibit discharges to sources of drinking water based on carcinogenicity concerns associated with ethylbenzene. Thus, this level will allow persons subject to the Act to determine whether a given discharge to sources of drinking water or exposure to people involving these chemicals is subject to the warning requirement and discharge prohibition provisions of the Act related to the risk of cancer (Health and Safety Code sections 25249.6).

Although section 25703 describes principles and assumptions for conducting risk assessments to derive safe harbor levels, many businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees needs the ability to determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Given the wide use of several of the chemicals covered by this regulation, the absence of this regulation would leave numerous businesses without an efficient way of determining if they are in compliance with the Act without the expenditure of significant resources on their part.

LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not pose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. It should be noted that Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.

REFERENCES

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