

**Response to Comments Pertaining to the Notice of Intent to List  
Methyl Isobutyl Ketone as Causing Reproductive Toxicity under Proposition 65**

**Office of Environmental Health Hazard Assessment  
California Environmental Protection Agency**

**March 2014**

On September 6, 2013, the Office of Environmental Health Hazard Assessment (OEHHA) published a Notice of Intent to List methyl isobutyl ketone (MIBK) under Proposition 65<sup>1</sup> as a chemical known to the State to cause reproductive toxicity. The action is based on the authoritative bodies provision<sup>2</sup> of the Proposition 65 implementing regulations and findings by the U.S. Environmental Protection Agency (U.S. EPA) in its 2003 Integrated Risk Information System (IRIS) entry for MIBK<sup>3</sup> and its 2003 document, "Toxicological Review of Methyl Isobutyl Ketone; In Support of Summary Information on the Integrated Risk Information System (IRIS)"<sup>4</sup>. OEHHA found that MIBK meets the criteria for listing provided in Title 27, Cal. Code of Regs., section 25306<sup>5</sup>. This document responds to comments received in response to the Notice of Intent to List MIBK under Proposition 65.

The conclusions in the U.S. EPA reports<sup>6,7</sup> regarding MIBK and reproductive toxicity (developmental endpoint) observed in animals exposed to MIBK satisfy the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.

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<sup>1</sup> The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 *et seq.*) hereinafter referred to as Proposition 65 or the Act.

<sup>2</sup> Title 27, Cal. Code of Regs., section 25306.

<sup>3</sup> U.S. EPA (U.S. Environmental Protection Agency) (2003). Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1). Integrated Risk Information System. Available online at: <http://www.epa.gov/iris/subst/0173.htm>.

<sup>4</sup> U.S. EPA (2003). Toxicological Review of Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-03/002 U.S. EPA, Washington DC, September. Available online at: <http://www.epa.gov/iris/toxreviews/0173tr.pdf>.

<sup>5</sup> All further references are to sections of Title 27, of the California Code of Regulations, unless indicated otherwise.

<sup>6</sup> U.S. EPA (2003). Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1). Integrated Risk Information System. Available online at: <http://www.epa.gov/iris/subst/0173.htm>.

<sup>7</sup> U.S. EPA (2003). Toxicological Review of Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-03/002 U.S. EPA, Washington DC, September. Available online at: <http://www.epa.gov/iris/toxreviews/0173tr.pdf>.

U.S. EPA<sup>8</sup> concluded:

“The developmental effects in rats and mice after gestational inhalation exposure are considered to be the most clearly adverse effects in the animal database.”  
(page 42)

“... delayed ossification in rats and mice and reduced fetal body weight and increased fetal death in mice were identified as the critical effects in a substantial database of repeat-dose inhalation studies.” (page 36)

“An RfC of 3 mg/m<sup>3</sup> was derived on the basis of effects observed in fetuses after repeated exposure on gestation days 6 to 15 (Tyl et al., 1987). The RfC was based on developmental effects in fetuses reported in a toxicity assay in which maternal exposure occurred only during gestation.” (page 41)

U.S. EPA developed an inhalation reference concentration (RfC) based on developmental toxicity manifested as reduced fetal body weight, skeletal variations, and increased fetal death in mice, and skeletal variations in rats<sup>9</sup>.

Comments responsive to the Notice of Intent to List were submitted by the Ketones Panel of the American Chemistry Council (ACC), and included a re-submission of comments previously submitted in response to a Request for Relevant Information on MIBK published on March 15, 2013<sup>10</sup>.

Comments on the Notice of Intent to List are summarized below, followed by OEHHA's responses.

### **Sufficiency of Evidence Criteria for “as causing reproductive toxicity”**

#### Comment:

The ACC comments state that the “2003 IRIS assessment does not provide sufficient basis for the Proposition 65 listing since it failed to consider relevant and scientifically

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<sup>8</sup> U.S. EPA (2003). Toxicological Review of Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-03/002 U.S. EPA, Washington DC, September. Available online at: <http://www.epa.gov/iris/toxreviews/0173tr.pdf>.

<sup>9</sup> U.S. EPA (2003). Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1). Integrated Risk Information System. Available online at: <http://www.epa.gov/iris/subst/0173.htm>.

<sup>10</sup> Comments received on the Request for Relevant Information, and OEHHA's responses to those comments were made publicly available as of September 6, 2013, at [http://www.oehha.ca.gov/prop65/CRNR\\_notices/admin\\_listing/requests\\_info/031513mik.html](http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/031513mik.html).

valid data that were available at the time or that have since become available challenging USEPA's conclusion." The comments state specifically that:

- *"USEPA Failed to Consider the Researchers' Conclusion that the Reductions in Fetal Body Weight Was Not Treatment-Related." (sic)*
- *"The IRIS assessment provides no analysis of the fetal body weight data reported by Tyl et al., other than to report the findings of the study. Consequently, it is not clear what consideration USEPA gave to the conclusions of the study authors regarding the significance of the body weight data, if any."*

Response:

Contrary to the above statements, the U.S. EPA "Toxicological Review of Methyl Isobutyl Ketone; In Support of Summary Information on the Integrated Risk Information System (IRIS)"<sup>11</sup> states that:

- "The authors indicated that the reduction in rat fetal body weight was confounded by a skewed distribution of litter size, whereby higher doses had very small litters and smaller litters had varied mean weights across dose, while lower-dosed dams appeared to have larger litters and larger litters showed a dose-dependence in mean weight. There was no statistically significant increase in the number of rat or mouse fetuses per litter. The authors decided the reductions in rat fetal body weight was[sic] not treatment-related." (page 16)

It is therefore clear that U.S. EPA did consider the authors' conclusions before determining that MIBK causes developmental toxicity. As noted above, U.S. EPA relied on reduced fetal body weight, skeletal variations and increased fetal death in mice, and skeletal variations in rats as the basis for developing a RfC. The authors of the Tyl et al. (1987) study did not question whether effects on fetal body weight in mice were treatment-related. Thus, there is no indication that the authors' conclusions constitute relevant data not considered by the authoritative body.

Comment:

Regarding consideration of data on reduced fetal weight in mice in the Tyl et al. (1987) study, ACC commented that:

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<sup>11</sup> U.S. EPA (2003). Toxicological Review of Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-03/002 U.S. EPA, Washington DC, September. Available online at: <http://www.epa.gov/iris/toxreviews/0173tr.pdf>.

- *“Among the offspring of the mouse dams, a reduction in fetal body weight only occurred at the highest dose for which the authors observed clear evidence of significant maternal toxicity (i.e., increase in deaths, clinical signs, and increased absolute and relative liver weight).”*

Response:

The study report by Tyl et al. (1987) states that “[c]linical observations, noted only in dams at 3000 ppm, and only during the exposure period, included irregular gait, paresis (partial hindlimb paralysis), hypoactivity, ataxia, negative toe pinch, unkempt fur, and lacrimation.” No quantitative or qualitative data are provided beyond these general statements. U.S. EPA noted these findings in the “Toxicological Review of Methyl Isobutyl Ketone; In Support of Summary Information on the Integrated Risk Information System (IRIS)”<sup>12</sup>:

- “Maternal clinical signs observed in rats or mice included coordination loss, hindlimb weakness, paresis, irregular gait, hypoactivity, ataxia, unkempt fur, negative tail or toe pinch, piloerection, lacrimation, or red perioral encrustation. These clinical signs were observed only during the exposure period and only at 12,292 mg/m<sup>3</sup>. Three maternal deaths (12% of the animals in the group) occurred in mice exposed to 12,292 mg/m<sup>3</sup> after the first exposure on gestation day 6; no further deaths occurred in that group, and no exposure-related deaths occurred in the other mouse or rat exposure groups.”

As with the earlier comment, it is clear that U.S. EPA considered these parameters before concluding that MIBK causes developmental toxicity, and that this information does not constitute relevant data not considered by the authoritative body.

Comment:

The ACC commented that “USEPA’s Assessment Failed to Consider OECD Guidance for Prenatal Developmental Toxicity Studies Adopted in 2001,” and goes on to describe the guidance and U.S. EPA’s involvement in its development. The ACC further commented that “USEPA Failed to Consider Whether Potential Human Exposure Data Indicate the Need to Test Exposures Above 2 ml/L, as Outlined in Its 1991 Guidelines.” (capital letters in original)

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<sup>12</sup> U.S. EPA (2003). Toxicological Review of Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-03/002 U.S. EPA, Washington DC, September. Available online at: <http://www.epa.gov/iris/toxreviews/0173tr.pdf>.

Response:

The guidance cited by ACC pertains to the design and conduct of developmental toxicity studies, rather than to the interpretation of developmental toxicity data in the context of risk assessment. As discussed in OEHHA's response to the ACC comments on the Request for Relevant Information on MIBK<sup>13</sup>, such guidance does not provide any data on the toxicity of MIBK nor does it constrain U.S. EPA in any way in the doses used or the interpretation of data from a study that did not conform to these specific guidelines.

Comment:

The ACC commented that "USEPA's Assessment of MIBK Failed to Consider the Results of the Two-Generation Reproduction Study in Assessing the Potential for Developmental Effects." (capital letters in original) The comment specifically notes that:

- *"OECD guidance stresses the importance of considering results from reproduction and other relevant studies in interpreting developmental toxicity study results. The two-generation reproduction study by Nemec (2000) provides a robust data set for MIBK both in terms of sample size and evaluated endpoints. Its sound scientific quality make it a relevant study from which to assess potential developmental effects – particularly in light of the excessively high doses used in the study by Tyl et al. USEPA's IRIS assessment does not include such consideration."*

Response:

As noted in OEHHA's response to the ACC comments on the Request for Relevant Information on MIBK<sup>14</sup>, the study by Nemec (2000) was considered by U.S. EPA, which identified it as WIL Research Laboratories (2000) and discussed it in both of the documents that serve as the basis for formal identification of MIBK as causing reproductive toxicity<sup>15,16</sup>. As expressed in the IRIS entry for MIBK: "The Tyl et al. (1987) developmental toxicity study was identified as the principal study and is described

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<sup>13</sup> Available online at

[http://oehha.ca.gov/prop65/CRNR\\_notices/admin\\_listing/intent\\_to\\_list/pdf\\_zip/090613MIBKresponseComs.pdf](http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/pdf_zip/090613MIBKresponseComs.pdf)

<sup>14</sup> *Ibid.*

<sup>15</sup> U.S. EPA (2003). Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1). Integrated Risk Information System. Available online at: <http://www.epa.gov/iris/subst/0173.htm>.

<sup>16</sup> U.S. EPA (2003). Toxicological Review of Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-03/002 U.S. EPA, Washington DC, September. Available online at: <http://www.epa.gov/iris/toxreviews/0173tr.pdf>.

below; the WIL Research Laboratories (2000) reproductive toxicity study is presented to support the principal study.”<sup>17</sup>

Comment:

ACC comments that “[m]ore recent interpretation of skeletal variations in laboratory animal tests suggest that they should not be considered adverse,” citing a 2007 publication by Carney and Kimmel that reviews the underlying mechanisms for delayed ossification and other skeletal variations in laboratory animals and evaluates the different scenarios in which they have been observed. The authors of that review conclude that “these minor variations would not generally be considered adverse in and of themselves but should be interpreted in the context of other maternal and fetal findings, information on normal skeletogenesis patterns, mode of action of the test agent, and historical control incidence.” ACC states that no such considerations were included in U.S. EPA’s IRIS assessment.

Response:

As noted by ACC in the introduction to their comments, U.S. EPA stated in the “Toxicological Review of Methyl Isobutyl Ketone; In Support of Summary Information on the Integrated Risk Information System (IRIS)”<sup>18</sup> that:

- “When evaluating the critical effect for MIBK, EPA used a weight-of-evidence approach and considered the totality of effects at the highest concentration as co-critical (delays in ossification, decreases in fetal body weight, and increased fetal death).”

U.S. EPA also considered factors such as maternal toxicity and litter size before formally identifying MIBK as causing developmental toxicity. This approach is consistent with that suggested by Carney and Kimmel, that “these minor variations would not generally be considered adverse in and of themselves but should be interpreted in the context of other maternal and fetal findings”. It should also be noted that the cited paper represents the judgment of two individual scientists, and does not provide any data on the toxicity of MIBK.

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<sup>17</sup> U.S. EPA (2003). Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1). Integrated Risk Information System. Available online at: <http://www.epa.gov/iris/subst/0173.htm>.

<sup>18</sup> U.S. EPA (2003). Toxicological Review of Methyl Isobutyl Ketone (MIBK) (CASRN 108-10-1); In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-03/002 U.S. EPA, Washington DC, September. Available online at: <http://www.epa.gov/iris/toxreviews/0173tr.pdf>.

OEHHA is not permitted to substitute its scientific judgment for that of the authoritative body<sup>19</sup>, nor can OEHHA substitute the judgment of other scientists for that of the authoritative body. The U.S. EPA has identified MIBK as causing developmental toxicity and OEHHA finds that decision is sufficiently supported by the totality of the record.

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<sup>19</sup> Final Statement of Reasons, Title 22 (now 27) California Code of Regulations, Section 12306 (now 25306). Available online at: [http://www.oehha.ca.gov/prop65/law/pdf\\_zip/12306FSRFeb1990.pdf](http://www.oehha.ca.gov/prop65/law/pdf_zip/12306FSRFeb1990.pdf). ExxonMobil Corp. v. OEHHA (2009) 169 Cal.App.4<sup>th</sup> 1264; Western Crop Protection v Davis (2000) 80 Cal.App.4<sup>th</sup> 741.