SUMMARY OF FINDINGS

The cancer potency was estimated for fumonisin B₁ using an expedited method. The dose-response data used in the analysis was generated by the National Toxicology Program ([NTP], 2001a; b) and summarized by Gold and colleagues (Gold & Zeiger, 1997; Gold, 2007) in the Carcinogenic Potency Database (CPDB). The expedited method represents the first level of a three-tiered risk assessment procedure currently in place for development of cancer potencies and Proposition 65 “No Significant Risk Levels” (NSRLs) and has been shown to produce reliable potency values (OEHHA, 1992; Hoover et al., 1995). Values generated using the expedited method may be reevaluated if scientific considerations indicate that more detailed analysis associated with a conventional risk assessment is warranted. Under the expedited method, the upper 95 percent confidence bound on the linear term of the multistage model fit to cancer dose response data is taken as the cancer potency estimate. The derivation takes into account species differences and length of the bioassay. The Proposition 65 NSRL is defined in regulation as the daily level posing a $10^{-5}$ lifetime risk of cancer. The cancer potency estimate and the corresponding NSRL for fumonisin B₁ are given in Table 1.

Table 1. Cancer potency and NSRL

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Human cancer potency (mg/kg-day)$^{-1}$</th>
<th>NSRL (μg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fumonisin B₁</td>
<td>0.48</td>
<td>1.5</td>
</tr>
</tbody>
</table>

INTRODUCTION

This report describes the derivation of the cancer potency and “No Significant Risk Level” (NSRL) for fumonisin B₁ (CAS number 116355-83-0). The expedited method was applied in the derivation and is summarized below (OEHHA, 1992; Hoover et al., 1995; Title 27, California Code of Regulations, section 25705(d)$^1$). The studies used for the potency derivation and the relevant data are described and the basis for selecting the cancer potency estimate is discussed.

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$^1$ All further references are to Title 27 of the California Code of Regulations unless otherwise indicated.
EXPEDITED METHOD

Overview

In a typical, non-expedited assessment, a full literature search is undertaken to locate all data on the carcinogenicity and dose response characteristics of the compound. This is followed by a review of the pharmacokinetic and mechanistic (e.g., genotoxicity) data, and all adequate bioassays. Occasionally there are data to support a pharmacokinetic analysis in the derivation of target dose estimates, or a dose response model different from the default. The expedited method (Section 25705(d)) is consistent with default quantitative risk assessment procedures for Proposition 65 (Section 25703), but differs from the usual practice in two ways. First, it relies on cancer bioassays summarized in the Carcinogenic Potency Database (CPDB), developed by Gold and colleagues (Gold and Zeiger, 1997; Gold, 2007). Second, under the expedited method, the choice of the multistage model is automatic and pharmacokinetic adjustments are not employed.

The expedited method has been shown to be a reliable means for generating potency values and NSRLs in a timely and efficient manner (OEHHA, 1992; Hoover et al., 1995). As described in Section 25705(d), an NSRL generated using the expedited method may be reevaluated if scientific considerations indicate that more detailed analysis associated with a conventional risk assessment is warranted.

Underlying assumptions

The expedited method for potency estimation incorporates the following assumptions:

- The dose-response relationship for carcinogenic effects in the most sensitive species tested is representative of that in humans.
- Observed experimental results can be extrapolated across species by use of the interspecies factor based on surface area scaling.
- The dose to the tissue giving rise to a tumor is assumed to be proportional to the administered dose.
- The multistage polynomial can be used to extrapolate potency outside the range of experimental observations to yield estimates of low dose potency.
- Cancer hazard increases with the third power of age.

Data set selection

The following criteria are used for data selection:

- Data sets with statistically significant increases in cancer incidence with dose are used.
- When several studies are available, and one study stands out as being of higher quality due to numbers of dose groups, magnitude of the dose applied, duration
of study, or other factors, the higher quality study is chosen as the basis for potency calculation.

- Potency is derived from data sets that tabulate malignant tumors, combined malignant and benign tumors, or tumors that would have likely progressed to malignancy.

**Linearized multistage model:**

Cancer potency is defined as the slope of the dose response curve at low doses. Following the default approach, the linearized multistage polynomial (Anderson et al., 1983; California Department of Health Services [CDHS], 1985; U.S. Environmental Protection Agency [U.S. EPA], 2002) describes the dose response relationship:

\[
\text{Probability of cancer} = 1 - \exp\left[-(q_0 + q_1d + q_2d^2 + \ldots)\right]
\]

with constraints, \(q_i \geq 0\) for all \(i\), and where \(d\) is the lifetime dose rate and \(q_i\) are parameters of the model, which are taken to be constants and are estimated from the animal cancer bioassay data. With five dose groups, as is the case with the fumonisin B\(_1\) male rat study analyzed here, the default linearized multistage model defaults to a fourth order polynomial with five parameters, \(q_0, \ldots, q_4\). The parameter \(q_0\) represents the background lifetime incidence of the tumor. The parameter \(q_1\) is, for small doses, the ratio of excess lifetime cancer risk to the average daily dose received. The upper 95% confidence bound on \(q_1\), estimated by maximum likelihood techniques, is referred to here as \(q_{1(UCB)}\) (Crump et al. 1977; Crump 1984). When the experiment duration is at least the natural life span of the animals, the parameter \(q_{1(UCB)}\) is taken as the animal cancer potency.

**Adjustment for less than lifetime exposure**

To estimate the animal cancer potency \((q_{\text{animal}})\) from experiments of duration \(T_e\), which is less than the natural life span of the animals \((T; \text{assumed to be 104 weeks for rats and mice [Gold & Zeiger 1997]})\), it is assumed that the lifetime incidence of cancer increases with the third power of age:

\[
q_{\text{animal}} = q_{1(UCB)} \cdot (104/T_e)^3
\]

**Multistage Weibull model:**

In some cases survival in the bioassay is inadequate, and the number of animals subject to late occurring tumors is significantly reduced. In such situations, the above described default procedure can inaccurately estimate the potency. A time-dependent model fit to individual animal data (i.e., tumor status and time of death for each animal under study) may provide better potency estimates. When there is an indication that survival is poor, a time-dependent analysis is employed using the multistage-in-dose Weibull-in-time (multistage Weibull) model. This model is an extension of the form given above (Equation 1), with the probability of tumor \((P(t,d))\) by time \(t\) and lifetime dose rate \(d\) given as:
Probability of cancer = 1 - \text{exp}\left[-(q_0 + q_1d + q_2d^2 + \ldots)(t-t_0)^k\right] \quad (3)

with \(q_i \geq 0\), for all \(i\), and \(0 \leq t_0 < t\), where \(t_0\) is commonly interpreted as the latency period, and \(k\) is the age exponent. In this case, carcinogenic potency for animals is derived by applying a maximum likelihood modeling approach to estimate the parameters \((q_i, t_0, \text{and } k)\). Using the multistage Weibull model, the animal cancer potency, \(q_{\text{animal}}\), is defined as the upper 95% confidence bound on \(q_1\) estimated at 104 weeks, the assumed standard lifetime for rats and mice.

**Interspecies scaling**

Once a potency value is estimated in animals following the techniques described above, human potency is estimated. A dose in units of milligram per unit surface area is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise (CDHS, 1985). Under this assumption, scaling to the estimated human potency \(q_{\text{human}}\) can be achieved by multiplying the animal potency \(q_{\text{animal}}\) by the ratio of human to animal body weights \((b_{wh}/b_{wa})\) raised to the one-third power when animal potency is expressed in units \((\text{mg/kg-day})^{-1}\) and body weight is expressed in kilograms:

\[
q_{\text{human}} = q_{\text{animal}} \times (b_{wh} / b_{wa})^{1/3} \quad (4)
\]

**Calculation of No Significant Risk Level**

The intake level (\(I\), in \(\text{mg/day}\)) associated with a cancer risk \(R\), from exposure is:

\[
I = \frac{R \times b_{wh}}{q_{\text{human}}} \quad (5)
\]

where \(b_{wh}\) is the human body weight in kilograms, and \(q_{\text{human}}\) is the cancer potency estimate for humans in units \((\text{mg/kg-day})^{-1}\). Daily intake levels associated with lifetime cancer risks above \(10^{-5}\) exceed the NSRL for cancer under Proposition 65 (Section 25703). Thus for a 70 kg person, the NSRL in units \(\mu\text{g/day}\) is given by:

\[
\text{NSRL} = \frac{10^{-5} \times 70 \text{ kg}}{q_{\text{human}}} \times 1000 \mu\text{g/mg}. \quad (6)
\]

**DERIVATION OF HUMAN CANCER POTENCY VALUE AND NSRL FOR FUMONISIN B\(_1\)**

The CPDB summarizes several fumonisin B\(_1\) cancer bioassays with diet as the exposure route: studies conducted by Gelderblom \textit{et al.}, (1991; 2001) and bioassays by the National Toxicology Program (NTP, 2001a). The Gelderblom \textit{et al.} (1991) study in male rats had a control group and one dose group (2 mg/kg, estimated by CPDB), with 25 animals per group. Because of interim sacrifices, the number of animals at risk for developing tumors was reduced. The CPDB tabulates incidence data for liver hepatocellular tumors of 3/5 and 7/10 for two of the interim sacrifice points, compared to 0/5 for controls at each time point. The Gelderblom \textit{et al.} (2001) study included more...
dose groups (0, 0.04, 0.4 and 1 mg/kg, CPDB estimates), with 20 animals per group. No statistically significant increases in tumors were reported for this study in the CPDB. The NTP (2001a; b) studies in male and female rats and mice had five dose groups with 50 animals per group. The doses in the NTP studies ranged between 0.25 mg/kg and 7.5 mg/kg for male rats, and 0.7 to 12.4 mg/kg for female mice (the two sex/species combinations with statistically significant findings). The NTP studies are more reliable for dose response analysis, based on the statistically significant findings, the greater number of dose groups, the dose range covered, and the numbers of animals per group.

NTP (2001a) exposed groups of 50 male and 50 female F344/N rats and B6C3F1 mice to fumonisin B1 for 105 weeks with feed concentrations of 0, 5, 15, 50, or 150 ppm fumonisin B1 for male rats; and 0, 5, 15, 50 or 80 ppm fumonisin B1 for female mice. The average daily doses were reported by NTP to be 0.25, 0.76, 2.5, or 7.5 mg/kg for exposed male rats and 0.7, 2.1, 7.1, or 12.4 mg/kg for exposed female mice.

NTP found clear evidence of neoplastic effects based on the observation of renal tubule adenomas or carcinomas (combined) in male rats and hepatocellular adenomas or carcinomas (combined) in female mice. No treatment related tumors were observed in female rats or male mice. In female mice, the survival rates between the highest dose group and all other dose groups were significantly different. To account for the differences in survival rates, a time-to-tumor approach (i.e., the multistage Weibull model) was employed to analyze the individual animal data for female mice (obtained from NTP, 2001b). For male rats, the linearized multistage model was used because the survival rates were similar across all dose groups.

The dose-response data for male rats and female mice are summarized in Tables 2 and 3. Table 4 provides the corresponding animal and human cancer potency estimates, along with the applicable interspecies scaling and experiment duration adjustment factors. The average body weights of 0.450 kg for male rats and 0.0245 kg for female mice were calculated based on the data reported by NTP (2001a) for control animals. As indicated in Table 4, the most sensitive sex, species and site is male rat kidney and the potency derived from these data was selected as the basis for the final potency estimate. Example calculations (using Equations 4 and 6) for the male rat are shown below:

\[ q_{\text{human}} = 0.08960 \times \left( \frac{70}{0.450} \right)^{1/3} = 0.48 \, \text{(mg/kg-day)}^{-1} \]

\[ \text{NSRL} = \frac{10^{-6} \times 70 \, \text{kg}}{0.48 \, \text{(mg/kg-day)}^{-1}} \times 1000 \, \mu\text{g/mg} = 1.5 \, \mu\text{g/day} \]

The human cancer potency for fumonisin B1 is estimated to be 0.48 (mg/kg-day)\(^{-1}\) and the associated NSRL is 1.5 μg/day.

Expedited NSRL for Fumonisin B1

October 2009
OEHHA
Table 2: Incidence of renal tubule tumors in male F334/N rats treated with fumonisin B₁ via diet (NTP, 2001a; b).

<table>
<thead>
<tr>
<th>Feed concentration¹ (ppm)</th>
<th>Average dose¹ (mg/kg-day)</th>
<th>Renal tubule adenomas and carcinomas, (combined)²</th>
<th>Statistical significance³</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0/42</td>
<td>p = 0.0001⁴</td>
</tr>
<tr>
<td>5</td>
<td>0.25</td>
<td>0/34</td>
<td>p = 1.00</td>
</tr>
<tr>
<td>15</td>
<td>0.76</td>
<td>0/40</td>
<td>p = 1.00</td>
</tr>
<tr>
<td>50</td>
<td>2.5</td>
<td>9/38</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>150</td>
<td>7.5</td>
<td>15/41</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

1. Doses reported by NTP (2001a).
2. Incidence of renal tubule adenoma or carcinoma (combined) from NTP (2001a; 2001b). The denominator is reported as the effective number, and represents the number of rats alive at the time of the appearance of the first renal tubule adenoma or carcinoma (day 587, based on the individual animal data for fumonisin B₁ available from NTP [2001b]).
3. The p-values from pairwise comparison with controls (Fisher Exact Test).
4. Trend test p-values from the poly-3 test (NTP, 2001a).
Table 3: Incidence of hepatocellular tumors in female B6C3F1 mice treated with fumonisin B1 via diet (NTP, 2001a; b).

<table>
<thead>
<tr>
<th>Feed concentration (ppm)</th>
<th>Average dose (mg/kg-day)</th>
<th>Hepatocellular adenoma or carcinoma (combined)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>5/47</td>
<td>p = 0.00014</td>
</tr>
<tr>
<td>5</td>
<td>0.7</td>
<td>3/48</td>
<td>p = 0.345N</td>
</tr>
<tr>
<td>15</td>
<td>2.1</td>
<td>1/48</td>
<td>p = 0.097N</td>
</tr>
<tr>
<td>50</td>
<td>7.1</td>
<td>19/47</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>80</td>
<td>12.4</td>
<td>39/45</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

1. Doses reported by NTP (2001a).
2. Incidence of hepatocellular adenoma or carcinoma (combined) from NTP (2001a; b). The denominator reflects the number of animals examined histologically for tumors. Effective number (i.e., number of animals alive at first appearance of tumor) is not reported for female mice because a time-dependent analysis was required.
3. The \( p \)-values from pairwise comparison with controls (Fisher Exact Test). An "N" after the \( p \)-value signifies that the incidence in the dose group is lower than that in the control group.
4. Trend test \( p \)-values from the poly-3 test (NTP, 2001a).

Table 4: Values used in calculating human cancer potency for fumonisin B1.

<table>
<thead>
<tr>
<th>Sex, species, site</th>
<th>Animal cancer potency ((q_{animal})) (mg/kg-day)(^{-1})</th>
<th>Interspecies scaling factor (unitless)</th>
<th>Correction for experiment duration (unitless)</th>
<th>Human cancer potency ((q_{human})) (mg/kg-day)(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male rat renal tubule adenoma and carcinoma (combined)</td>
<td>0.08960</td>
<td>((70/0.450)^{1/3})</td>
<td>((104/104)^3)</td>
<td>0.48</td>
</tr>
<tr>
<td>Female mouse hepatocellular adenoma and carcinoma (combined)</td>
<td>0.01889</td>
<td>((70/0.0245)^{1/3})</td>
<td>(-1)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

1. The cancer potency for female mice was estimated using the multistage Weibull model; the correction for experiment duration is incorporated into the time-dependent analysis. **Bold** indicates basis for NSRL.
REFERENCES


U.S. Environmental Protection Agency (U.S. EPA, 2002). Health Assessment of 1,3-Butadiene. National Center for Environmental Assessment, Washington, DC. EPA/600/P-98/001F.