CHEMICAL MEETING THE CRITERIA FOR LISTING AS CAUSING CANCER VIA THE AUTHORITATIVE BODIES MECHANISM

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The chemical listed in the table below meets the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

The National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC) are two of five institutions that have been identified as authoritative bodies for the purposes of Proposition 65 (22 CCR 12306(m)). NTP and IARC have identified the chemical in the table below as causing cancer. The Office of Environmental Health Hazard Assessment (OEHHA) has found that this chemical has been "formally identified" as causing cancer according to the regulations covering this issue (22 CCR 12306(d)): The chemical below is the subject of reports published by the authoritative bodies that conclude that the chemical causes cancer. Also, the documents specifically and accurately identify the chemical and meet one or more of the criteria outlined in 22 CCR 12306(d)(2).

OEHHA also finds that the criteria given in regulation for "as causing cancer" (22 CCR 12306(e)) have been satisfied for the chemical in the table below. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative bodies in making their findings that the specified chemical causes cancer. A brief discussion of the relevant carcinogenesis studies providing evidence for the findings is presented below. The statement in bold reflects data and conclusions that satisfy the criteria for the sufficiency of evidence for carcinogenicity (22 CCR 12306(e)). The full citations for the authoritative body documents are given in this report.

Chemical Meeting the Criteria for Listing as Causing Cancer

Chemical	CAS No.	Chemical Use	Reference
Fumonisin B_1	116355-83-0	Mycotoxin, produced by fungus *Fusarium moniliforme*, found in corn and corn-based products.	NTP (2001) IARC (2002)

Fumonisin B_1 (CAS No. 116355-83-0)

Increased incidence of malignant and combined malignant and benign tumors in male rats; increased incidence of malignant and combined malignant and benign tumors in female mice.

The National Toxicology Program (NTP, 2001) has concluded that there is clear evidence of the carcinogenic activity of fumonisin B_1 in male F344/N rats and in female B6C3F_1 mice. The basis for the NTP finding was increased renal tumors in male rats and increased hepatocellular tumors in female mice. The International Agency for Research on Cancer (IARC, 2002) has also evaluated the available animal studies (including those from NTP) and has concluded that there is sufficient evidence in experimental animals for the carcinogenicity of fumonisin B_1. IARC (2002) has classified fumonisin B_1 in Group 2B, possibly carcinogenic to humans. The basis for the IARC finding was increased hepatocellular adenomas and carcinomas in female mice, hepatocellular carcinomas in one male rat study, and a rare highly malignant variant of renal tubular carcinomas in a second male rat study. The relevant studies are described below.

As reviewed by IARC, Gelderblom *et al.* (1991) administered fumonisin B_1 to male BD IX rats (n=25) via diet for 26 months. A control group (n=25) was fed a basal diet, and control and treated animals were sacrificed at designated time periods. In the 15 treated rats that died or were sacrificed between 18 and 26 months, hepatocellular carcinomas were observed in 10/15 rats. Four rats developed metastases (to the heart, lungs or kidneys). No carcinomas were observed in control animals.

NTP (2001) exposed B6C3F_1 mice and F344/N rats to fumonisin B_1 via diet for two years. In treated female mice, increased incidences of hepatocellular adenoma (5/47, 3/48, 1/48, 16/47, 31/45), hepatocellular carcinoma (0/47, 0/48, 0/48, 10/47, 9/45) and combined hepatocellular adenoma or carcinoma (5/47, 3/48, 1/48, 19/47, 39/45) were observed. The increases were statistically significant at the two highest dose levels. The NTP (2001) found that decreased survival in the highest dose group was probably due to the increased incidence of hepatocellular neoplasms. No increases in tumor incidence were observed in male mice.

In male rats, statistically significant increases in renal tubule adenoma and in renal tubule carcinoma were observed. The incidence of renal tubule carcinoma was 0/48, 0/40, 0/48, 7/48, and 10/48 for control, low-, mid-, midhigh- and high-dose groups, respectively. The combined incidence of renal tubule adenoma or carcinoma was 0/48, 0/40, 0/48,

9/48, and 15/48. No neoplastic effects were seen in female rats exposed to fumonisin B_1. The NTP (2001) commented that "it appears that female rats could have tolerated somewhat higher exposure concentrations."

IARC (2002) cites a re-evaluation of the renal pathology in the NTP male rat study (Hard *et al.*, 2001). Hard *et al.* (2001) found that the incidence of adenomas in the two highest dose groups was 4/48 and 8/48, respectively. The incidence of carcinomas was 6/48 and 10/48 for the two groups, respectively. In addition, 2/8 and 5/8 of the carcinomas in the midhigh- and high-dose groups, respectively, metastasized to the lungs. IARC (2002) wrote: "Only one of the 18 carcinomas displayed the conventional reasonably differentiated phenotype. Cellular pleomorphisms were noticed in 3/8 and 1/10 carcinomas in rats fed 50 and 150 mg/kg, respectively. Among the carcinomas observed in these studies, 61% were an anaplastic variant."

REFERENCES:

Hard GC, Howard PC, Kovatch RM, Bucci TJ (2001). Rat kidney pathology induced by chronic exposure to fumonisin B_1 includes rare variants of renal tubule tumor. *Toxicol Pathol* **29**: 379-386.

Gelderblom WCA, Kriek NPJ, Marasas WFO, Thiel PG (1991). Toxicity and carcinogenicity of the *Fusarium moniliforme* metabolite, fumonisin B_1, in rats. *Carcinogenesis* **12**:1247-1251.

International Agency for Research on Cancer (IARC, 2002). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* Volume 82: 301-366. *Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene.* IARC, Lyon France.

National Toxicology Program (NTP, 2001). *Toxicology and Carcinogenesis Studies of Fumonisin B_1 (CAS No. 116355-83-0) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies).* NTP Technical Report Series No. 496, NIH Publication No. 01-3955. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NTP, Research Triangle Park, NC.