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

PACKAGE 22a
August 5, 2005

Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Nitrapyrin meets the criteria for listing under Proposition 65[1] via the authoritative bodies listing mechanism as known to the State to cause cancer. The regulatory requirements for listing by this mechanism are set forth in Title 22, California Code of Regulations, Section 12306[2] and 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.

U.S. Environmental Protection Agency (U.S. EPA) is one of five institutions that have been identified as authoritative bodies for identification of chemicals as causing cancer for the purposes of Proposition 65 (§12306(1)). U.S. EPA has identified nitrapyrin as causing cancer. The Office of Environmental Health Hazard Assessment (OEHHA) has found that nitrapyrin has been "formally identified" as causing cancer as required by §12306(d). Nitrapyrin is the subject of a report published by the authoritative body that concludes that the chemical causes cancer. Also, the U.S. EPA document specifically and accurately identifies the chemical, and the document meets one or more of the criteria outlined in §12306(d)(2).

OEHHA also finds that the criteria given in regulation for "as causing cancer" (§12306(e)) have been satisfied for nitrapyrin. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative body in making its finding that the specified chemical causes cancer. A brief discussion of the relevant carcinogenesis studies providing evidence for the finding is presented below. The statement in bold reflects data and conclusions that satisfy the criteria for the sufficiency of evidence for carcinogenicity (§12306(e)). The full citation for the U.S. EPA document is given in this report.

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[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5

[2] All further references are to Title 22 of the California Code of Regulations, unless otherwise indicated.

Chemical Meeting the Criteria for Listing as Known to the State to Cause Cancer

Chemical	CAS No.	Chemical Use	Reference
Nitrapyrin	1929-82-4	Nitrogen stabilizer for ammonia and urea nitrogen fertilizers.	U.S. EPA (2000)

Nitrapyrin (CAS No. 1929-82-4)

Increased incidence of malignant and combined malignant and benign tumors in male and female mice with tumors at multiple and uncommon sites.

U.S. EPA (2000) has concluded that nitrapyrin [2-chloro-6-(trichloromethyl) pyridine] is "likely to be carcinogenic in humans." The U.S. EPA (2000) evaluation was the second review of nitrapyrin. The chemical was first evaluated in 1992 at which time U.S. EPA (1992) concluded that renal tubular adenomas and adenocarcinomas observed in male rats were associated with α_{2u}-globulin-induced nephropathy and that a mouse study was inadequate for carcinogenicity assessment. Nitrapyrin was classified in Group D, not classifiable as to human carcinogenicity. In 2000, nitrapyrin was re-evaluated to assess newly completed mouse carcinogenicity studies. These studies are briefly described below.

Male and female $B6C3F_1$ mice (50/group/sex) received nitrapyrin via diet for two years. Multiple tumors developed in both male and female mice. In male mice, tumors of the liver, stomach and epididymis were increased. There were statistically significant increases in the incidences of hepatocellular adenomas (12/49, 19/50 and 45/48 [$p< 0.01$] for control, low- and high-dose animals, respectively) and combined hepatocellular adenomas or carcinomas (17/49, 20/50, 46/49 [$p< 0.01$]). The incidence of hepatocellular carcinomas (7/49, 3/50, 12/49) was also increased, but did not reach statistical significance. Increases in squamous cell tumors of the nonglandular stomach (papillomas: 1/43, 9/49 and 12/36 [$p<0.01$]; carcinomas: 0/43, 0/49 and 3/38 [$p<0.01$]; combined papillomas and carcinomas: 1/43, 9/49 and 15/38 [$p<0.01$]) were statistically significant. U.S. EPA (2000) noted that these are rare tumors. A statistically significant increase in testicular undifferentiated epididymal sarcomas (0/40, 2/48 and 4/33 [$p< 0.05$]) was also observed in high-dose male rats. U.S. EPA (2000) noted the finding in the high dose group was significant and also considered the increase in sarcomas at the low dose (2/48) to be biologically significant and noted that these were also rare tumors.

Nitrapyrin-treated female mice developed tumors of the stomach, liver, and Harderian gland. Incidences of stomach nonglandular squamous cell papillomas (1/47, 8/48

[p<0.05] and 21/48 [p<0.01] for control, low- and high-dose animals, respectively) and combined squamous cell papillomas or carcinomas of the nonglandular stomach (1/47, 8/48 [p<0.05], 22/48 [p<0.01]) were also significantly increased. The incidence of squamous cell carcinoma of the nonglandular stomach (0/47, 0/48, 2/48) was not statistically significant, but U.S. EPA (2000) considered the increase in carcinomas at the high dose (2/48) to be biologically significant. The incidences of these tumors were outside the historical control range (historical range for papillomas of the nonglandular stomach: 0-1%; for carcinomas: 0%). There were also statistically significant increases in the incidences of hepatocellular adenomas and combined adenomas and carcinomas in treated mice. The incidence of hepatocellular adenoma was 6/47, 27/48 [p<0.01] and 32/48 [p<0.01] for control, low- and high-dose groups, respectively. The combined incidence of adenomas or carcinomas was 6/47, 38/48 [p<0.01] and 33/48 [p<0.01]. The incidence of hepatocellular carcinoma (0/47, 1/48 and 2/48) was also increased although not significantly. In addition, statistically significant increases in Harderian gland adenomas (1/47, 8/48 and 9/48 [p<0.01]) were observed.

REFERENCES

U.S. Environmental Protection Agency (U.S. EPA, 1992). *Memorandum: Carcinogenicity Peer Review of Nitrapyrin.* Health Effects Division. September 14, 1992.

U.S. Environmental Protection Agency (U.S. EPA, 2000). Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Nitrapyrin (Second Review). Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. May 5, 2000.