CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986 (PROPOSITION 65)

REQUEST FOR RELEVANT INFORMATION ON CHEMICALS BEING CONSIDERED FOR LISTING BY THE AUTHORITATIVE BODIES MECHANISM:

ISOPYRAZAM, BETA-MYRCENE, PULEGONE, AND 3,3',4,4'-TETRACHLOROAZOBENZENE

February 10, 2012

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) is requesting information as to whether the chemicals *isopyrazam*, *beta-myrcene*, *pulegone*, and *3,3',4,4'-tetrachloroazobenzene* meet the criteria for listing as known to the State to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986.[1] This action is being proposed under the authoritative bodies listing mechanism.[2]

Chemicals Appearing to Meet Criteria for Listing as Known to Cause Cancer		
Chemical (CAS No.)	**Reference**	**Occurrence and Uses**
Isopyrazam (881685-58-1)	U.S. EPA (2011)	Pyrazole fungicide. Not registered by the U.S. EPA, but used in Central and South American on bananas to control black sigatoka (*Mycosphaerella fijiensis*).
beta-Myrcene (123-35-3)	NTP (2010a)	Component of certain essential oils, such as hop, bay, verbena, and lemongrass oils. Used to produce aroma and flavor chemicals, as a flavoring agent in food and beverages, and as a fragrance in cosmetics, soaps, and detergents.
Pulegone (89-82-7)	NTP (2011)	A constituent of pennyroyal, mint, and peppermint, and a component of certain essential oils. Used in flavoring food, drinks, and dental products, as a fragrance, and in herbal medicines.
3,3',4,4'-Tetrachloro-azobenzene (14047-09-7)	NTP (2010b)	Contaminant of 3,4-dichloroaniline and the related herbicides linuron, diuron, and propanil, and a degradation product of 3,4-dichloroaniline and chloroanilide herbicides.

Background on listing via the authoritative bodies mechanism: A chemical must be listed under the Proposition 65 regulations when two conditions are met:

[1] Commonly known as Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986 is codified in Health and Safety Code section 25249.5 *et seq*.
[2] See Health and Safety Code section 25249.8(b) and Title 27, Cal. Code of Regs., section 25306.

1) An authoritative body formally identifies the chemical as causing cancer (Section 25306(d)[3]).
2) The evidence considered by the authoritative body meets the sufficiency criteria contained in the regulations (Section 25306(e)).

However, the chemical is not listed if scientifically valid data which were not considered by the authoritative body clearly establish that the sufficiency of evidence criteria were not met (Section 25306(f)).

The National Toxicology Program (NTP) and the U.S. Environmental Protection Agency (U.S. EPA) are two of several institutions designated as authoritative for the identification of chemicals as causing cancer (Section 25306(m)).

OEHHA is the lead agency for Proposition 65 implementation. After an authoritative body has made a determination about a chemical, OEHHA evaluates whether listing under Proposition 65 is required using the criteria contained in the regulations.

OEHHA's determination: *Isopyrazam*, *beta-myrcene*, *pulegone*, and *3,3',4,4'-tetra-chloroazobenzene* each appear to meet the criteria for listing as known to the State to cause cancer under Proposition 65, based on findings of the NTP and U.S. EPA (NTP, 2010a; NTP, 2010b; NTP, 2011; U.S. EPA, 2011).

Formal identification and sufficiency of evidence for isopyrazam: In 2011, the U.S. EPA published a report on isopyrazam, entitled *Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Isopyrazam*, that concludes that the chemical causes cancer (U.S. EPA, 2011). This report appears to satisfy the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.

OEHHA is relying on the U.S. EPA's discussion of data and conclusions in the report that isopyrazam causes cancer. The U.S. EPA report concludes that isopyrazam is "likely to be carcinogenic to humans." Evidence described in the report includes studies showing that isopyrazam increased the incidences of thyroid follicular cell carcinomas and combined adenomas and carcinomas in male Wistar rats, and uterine endometrial adenocarcinomas in female Wistar rats.

Thus, the U.S. EPA (2011) has found that isopyrazam causes increased incidence of malignant and combined malignant and benign thyroid tumors in male rats and malignant tumors of the uterus in female rats.

Formal identification and sufficiency of evidence for beta-myrcene: In 2010, the NTP published a report on beta-myrcene (β-myrcene), entitled *Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*, that concludes that the chemical causes cancer (NTP, 2010a). This report appears to satisfy the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.

OEHHA is relying on the NTP's discussion of data and conclusions in the report that beta-myrcene causes cancer. The NTP (2010a) report concludes:

[3] All referenced sections are from Title 27 of the Cal. Code of Regulations.

> "Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity* of β-myrcene in male F344/N rats based on increased incidences of renal tubule neoplasms. There was *equivocal evidence of carcinogenic activity* of β-myrcene in female F344/N rats based on increased incidences of renal tubule adenoma. There was *clear evidence of carcinogenic activity* of β-myrcene in male B6C3F1 mice based on increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma. There was *equivocal evidence of carcinogenic activity* of β-myrcene in female B6C3F1 mice based on marginally increased incidences of hepatocellular adenoma and carcinoma."

Thus, the NTP (2010a) has found that beta-myrcene causes increased incidences of combined malignant and benign kidney tumors in male rats and malignant and combined malignant and benign liver tumors in male mice.

Formal identification and sufficiency of evidence for pulegone: In 2011, the NTP published a report on pulegone, entitled *Toxicology and Carcinogenesis Studies of Pulegone (CAS No. 89-82-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*, that concludes that the chemical causes cancer (NTP, 2011). This report appears to satisfy the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.

OEHHA is relying on the NTP's discussion of data and conclusions in the report that pulegone causes cancer. The NTP (2011) report concludes:

> "Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity* of pulegone in male F344/N rats administered 18.75, 37.5, or 75 (stop-exposure) mg/kg. There was *clear evidence of carcinogenic activity* of pulegone in female F344/N rats based on increased incidences of urinary bladder neoplasms. There was *clear evidence of carcinogenic activity* of pulegone in male and female B6C3F1 mice based on increased incidences of hepatocellular neoplasms (adenomas in both sexes and hepatoblastomas in males). Osteomas and osteosarcomas in female B6C3F1 mice may have been related to pulegone administration."

Thus, the NTP (2011) has found that pulegone causes increased incidences of combined malignant and benign rare urinary bladder tumors in female rats and combined malignant and benign liver tumors in male mice.

Formal identification and sufficiency of evidence for 3,3',4,4'-tetrachloroazo-benzene: In 2010, the NTP published a report on 3,3',4,4'-tetrachloroazobenzene (TCAB) entitled *Toxicology and Carcinogenesis Studies of 3,3',4,4'-Tetrachloroazo-benzene (TCAB) (CAS No. 14047-09-7) in Harlan Sprague-Dawley Rats and B6C3F1 Mice (Gavage Studies)*, that concludes that the chemical causes cancer (NTP, 2010b). This report appears to satisfy the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.

OEHHA is relying on the NTP's discussion of data and conclusions in the report that 3,3',4,4'-tetrachloroazobenzene causes cancer. The NTP (2010b) report concludes:

> "Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity* of TCAB in male Harlan Sprague-Dawley rats based on increased incidences of cystic keratinizing epithelioma of the lung, cholangiocarcinoma of the liver, and gingival squamous cell carcinoma of the oral mucosa. The increased incidences of follicular cell adenoma of the thyroid gland were also considered to be related to TCAB administration. The marginally increased incidence of malignant schwannoma may have been related to TCAB administration. There was *clear evidence of carcinogenic activity* of TCAB in female Harlan Sprague-Dawley rats based on increased incidences of cystic keratinizing epithelioma of the lung and gingival squamous cell carcinoma of the oral mucosa. The increased incidences of cholangiocarcinoma of the liver and squamous cell papilloma or squamous cell carcinoma (combined) of the forestomach were also considered to be related to TCAB administration. The marginally increased incidences of adenoma of the adrenal cortex may have been related to TCAB administration. There was *clear evidence of carcinogenic activity* of TCAB in male B6C3F1 mice based on increased incidences of carcinoma of the urethra and alveolar/bronchiolar neoplasms of the lung. The increased incidences of squamous cell carcinoma of the forestomach were also considered to be related to TCAB administration. The marginally increased incidence of carcinoma of the ureter may have been related to TCAB administration. There was *clear evidence of carcinogenic activity* of TCAB in female B6C3F1 mice based on increased incidences of fibrosarcoma and fibrosarcoma or malignant schwannoma (combined) of the skin. The increased incidences of carcinoma of the urethra, alveolar/bronchiolar neoplasms and cystic keratinizing epithelioma of the lung, and squamous cell carcinoma of the forestomach were also considered to be related to TCAB administration. The marginally increased incidences of malignant lymphoma may have been related to TCAB administration."

Thus, the NTP (2010b) has found that 3,3',4,4'-tetrachloroazobenzene causes increased incidences of malignant tumors at multiple sites in male rats, rare malignant tumors of the oral cavity in female rats, malignant tumors at multiple sites in male mice, and malignant tumors at multiple sites in female mice.

Request for relevant information: OEHHA is committed to public participation in its implementation of Proposition 65. OEHHA wants to ensure that its regulatory decisions are based on a thorough consideration of all relevant information. OEHHA is requesting comments as to whether these chemicals meet the criteria set forth in the Proposition 65 regulations for authoritative bodies listings.

After reviewing all comments received, OEHHA will determine whether the identified chemical meets the regulatory criteria for administrative listing. For chemicals determined to meet the listing criteria, OEHHA will proceed with the listing process and publish a Notice of Intent to List.

In order to be considered, **OEHHA must receive comments by 5:00 p.m. on Tuesday, April 10, 2012.** We encourage you to submit comments via e-mail, rather than in paper form. Comments transmitted by e-mail should be addressed to P65Public.Comments@oehha.ca.gov with "DCI" and the name of the chemical commented on in the subject line. Hard copy comments may be mailed, faxed, or delivered in person to the addresses below:

Mailing Address:	Ms. Cynthia Oshita Office of Environmental Health Hazard Assessment P.O. Box 4010, MS-19B Sacramento, California 95812-4010
Fax:	(916) 323-8803
Street Address:	1001 I Street Sacramento, California 95814

Comments received during the public comment period will be posted on the OEHHA web site after the close of the comment period.

Optional public forum: Upon request, OEHHA will schedule a public forum to provide individuals an opportunity to present oral comments on the possible listing of these chemicals. At the forum, the public may discuss the scientific data and other relevant information related to whether these chemicals meet the criteria for listing in the regulations.

The request for a public form must be submitted in writing to Cynthia Oshita of OEHHA via email at cynthia.oshita@oehha.ca.gov or to the attention of Cynthia Oshita at the address listed above no later than Monday, March 12, 2012. If a public forum is requested, a notice will be posted on the OEHHA web site at least ten days before the forum date. The notice will provide the date, time, location and subject matter to be heard. Notices will also be sent to those individuals requesting such notification.

If you have any questions, please contact Ms. Oshita at cynthia.oshita@oehha.ca.gov or at (916) 445-6900.

References

NTP (2010a). National Toxicology Program *Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*. Technical Report Series No. 557. NIH Publication No. 10-5898. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

NTP (2010b). National Toxicology Program. *Toxicology and Carcinogenesis Studies of 3,3',4,4'-Tetrachloroazobenzene (TCAB) (CAS No. 14047-09-7) in Harlan Sprague-Dawley Rats and B6C3F1 Mice (Gavage Studies)*. Technical Report Series No. 558. NIH Publication No. 11-5899. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

NTP (2011). National Toxicology Program. *Toxicology and Carcinogenesis Studies of Pulegone (CAS No. 89-82-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*. Technical Report Series No. 563. NIH Publication No. 11-5905. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

U.S. EPA (2011). U.S. Environmental Protection Agency. *Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Isopyrazam. PC Code 129222*. *Final Report*. Health Effects Division, Office of Pesticide Programs. February 8, 2011.