CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

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

NOTICE OF INTENT TO LIST A CHEMICAL BY THE "FORMALLY REQUIRED TO BE LABELED OR IDENTIFIED" MECHANISM: MITOXANTRONE HYDROCHLORIDE

NOVEMBER 7, 2014

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) intends to list mitoxantrone hydrochloride 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 "Formally Required to Be Labeled or Identified" listing mechanism[2].

Chemical	CAS No.	Toxicological Endpoint	Reference
Mitoxantrone hydrochloride*	70476-82-3	Cancer	FDA (2012)

*Note: This chemical has been listed under Proposition 65 as causing reproductive toxicity (developmental endpoint) since July 1, 1990.

Background on listing via the formally required to be labeled or identified mechanism: A chemical must be listed under Proposition 65[3] and its implementing regulations (Section 25902[4]) when a state or federal agency has formally required it to be labeled or identified as causing cancer or reproductive toxicity.

OEHHA is the lead agency for Proposition 65 implementation, and evaluates whether listing under Proposition 65 is required pursuant to the definitions set out in Section 25902.According to Section 25902(b):

- "'[F]ormally required' means that a mandatory instruction, order, condition, or similar command, has been issued in accordance with established policies and procedures of an agency of the state or federal government to a person or legal entity outside of the agency. The action of such agency may be directed at one

[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 25902.
[3] See Health and Safety Code section 25249.8(b).
[4] All referenced regulatory sections are from Title 27 of the Cal. Code of Regulations.

or more persons or legal entities and may include formal requirements of general application;"

- "'[L]abeled' means that a warning message about the carcinogenicity or reproductive toxicity of a chemical is printed, stamped, written, or in any other manner placed upon the container in which the chemical is present or its outer or inner packaging including any material inserted with, attached to, or otherwise accompanying such a chemical;"
- "'[I]dentified' means that a required message about the carcinogenicity or reproductive toxicity of the chemical is to be disclosed in any manner to a person or legal entity other than the person or legal entity who is required to make such disclosure"; and
- "As causing cancer" means: "For chemicals that cause cancer, the required label or identification uses any words or phrases intended to communicate a risk of cancer or tumors."

OEHHA's determination: *Mitoxantrone hydrochloride* has been identified and labeled to communicate a risk of cancer (FDA, 2012) in accordance with formal requirements by the US Food and Drug Administration (FDA). The FDA-approved label indicates that *mitoxantrone hydrochloride* therapy in patients with multiple sclerosis and in patients with cancer increases the risk of developing secondary acute myeloid leukemia (a type of cancer of the lymphohematopoietic system). NOVANTRONE® is a trade name of mitoxantrone hydrochloride.

Language from the FDA-approved product label which meets the requirements of Section 25902 is quoted below:

Mitoxantrone hydrochloride

Cancer Endpoint

FDA-approved label Reference ID 3105100 (FDA, 2012)

Under BOXED WARNING: "Secondary Leukemia: NOVANTRONE® therapy in patients with MS and in patients with cancer increases the risk of developing secondary acute myeloid leukemia."

Under WARNINGS:

General. **"**Topoisomerase II inhibitors, including NOVANTRONE, have been associated with the development of secondary acute myeloid leukemia and myelosuppression."

Secondary Leukemia. "NOVANTRONE® therapy increases the risk of developing secondary leukemia in patients with cancer and in patients with multiple sclerosis."

Request for comments: OEHHA is requesting comments as to whether this chemical meets the criteria set forth in the Proposition 65 regulations for listings via the formally required to be labeled or identified mechanism (Section 25902). Because these are ministerial listings, comments should be limited to whether FDA requires that *mitoxantrone hydrochloride* be labeled to communicate a risk of cancer or tumors. OEHHA cannot consider scientific arguments concerning the weight or quality of the

evidence considered by FDA when it established the labeling requirement and will not respond to such comments if they are submitted.

In order to be considered, **OEHHA must receive comments by 5:00 p.m. on December 8, 2014.** We encourage you to submit comments in electronic form, rather than in paper form. Comments transmitted by e-mail should be addressed to P65Public.Comments@oehha.ca.gov. Please include "mitoxantrone hydrochloride" in the subject line. Comments submitted in paper form may be mailed, faxed, or delivered in person to the address below.

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

If you have any questions, please contact Monet Vela at (916)323-2517 or Monet.Vela@oehha.ca.gov.

References

Food and Drug Administration (FDA, 2012). FDA approved drug label, Reference ID 3105100, approved 3-23-2012. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019297s035lbl.pdf