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 BEVACIZUMAB
OCTOBER 5, 2018

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) intends to list bevacizumab as known to the state to cause reproductive toxicity (developmental and female endpoints) 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
Bevacizumab	216974-75-3	Female reproductive toxicity Developmental toxicity	FDA (2018)

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 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

[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.

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 reproductive toxicity" means: "For chemicals that cause reproductive toxicity, the required label or identification uses any words or phrases intended to communicate a risk of reproductive harm to men or women or both, or a risk of birth defects or other developmental harm."

OEHHA's determination: *Bevacizumab* is a vascular endothelial growth factor-directed antibody indicated for the treatment of certain types of cancers. It has been identified and labeled to communicate a risk of reproductive harm (developmental and female endpoints) (FDA, 2018) in accordance with formal requirements by the US Food and Drug Administration (FDA). The FDA-approved label indicates that uses of *bevacizumab* have the potential to increase the risk of ovarian failure and may cause fetal harm. Avastin® is a trade name of bevacizumab.

Language from the FDA-approved product label (Reference ID: 4277004; FDA, 2018) which meets the requirements of Section 25902 is quoted below:

Bevacizumab
Reproductive Toxicity (Female and Developmental Endpoints)

Under HIGHLIGHTS OF PRESCRIBING INFORMATION
WARNINGS AND PRECAUTIONS:

- "Embryo-fetal Toxicity: Advise females of potential risk to fetus and need for use of effective contraception. (5.10, 8.1, 8.3)"
- "Ovarian Failure: Advise females of the potential risk. (5.11, 8.3)"

Under WARNINGS AND PRECAUTIONS:
"5.10 Embryo-fetal Toxicity
Avastin *[bevacizumab]* may cause fetal harm based on its mechanism of action and findings from animal studies. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGFR 2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the

potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with and for 6 months after the last dose of Avastin *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)].”*

“**5.11 Ovarian Failure**
The incidence of ovarian failure was 34% vs. 2% in premenopausal women receiving Avastin *[bevacizumab]* with chemotherapy as compared to those receiving chemotherapy alone for adjuvant treatment of a solid tumor. After discontinuing Avastin, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% of women receiving Avastin. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long-term effects of Avastin on fertility are unknown. Inform females of reproductive potential of the risk of ovarian failure prior to initiating Avastin *[see Adverse Reactions (6.1), Use in Specific Populations (8.3)].*

Under ADVERSE REACTIONS*:*
“Ovarian Failure [*See Warnings and Precautions (5.11)”*

Under USE IN SPECIFIC POPULATIONS:
“8.1 Pregnancy
Risk Summary
Avastin *[bevacizumab]* may cause fetal harm based on findings from animal studies and its mechanism of action. *[see Clinical Pharmacology (12.1)]*. Limited postmarketing reports describe cases of fetal malformations with use of Avastin in pregnancy; however, these reports are insufficient to determine drug associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects *[see Data]*. Furthermore, animal models link angiogenesis and VEGF and VEGFR-2 to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.”

“**8.3 Females and Males of Reproductive Potential**

Contraception

Females

Avastin *[bevacizumab]* may cause fetal harm when administered to a pregnant woman. *[see Use in Specific Populations (8.1).*] Advise female of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose of Avastin.”

Infertility

Females

Avastin *[bevacizumab]* increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to the first-dose of Avastin. Long-term effects of Avastin on fertility are not known.

In a clinical study of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in patients who received Avastin with chemotherapy (34%) compared patients who received chemotherapy alone (2%). After discontinuing Avastin with chemotherapy, recovery of ovarian function occurred in 22% of these patients. *[see Warnings and Precautions (5.11), Adverse Reactions (6.1*).]

Under **NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

“Bevacizumab may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea, as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.”

Under **PATIENT COUNSELING INFORMATION**

“Embryo-Fetal Toxicity: Advise female patients that Avastin *[bevacizumab]* may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)].* Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose of Avastin *[see Use in Specific Populations (8.3)].*

Ovarian Failure: Avastin may lead to ovarian failure. Advise patients of potential options for preservation of ova prior to starting treatment *[see Warnings and Precautions (5.11)].”*

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 this is a ministerial listing, comments should be limited to whether FDA requires that *bevacizumab* be labeled to communicate a risk of reproductive or developmental harm. 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 Monday, November 5, 2018.** Comments may be submitted electronically through our website at **https://oehha.ca.gov/comments**.

Comments submitted in paper form can be mailed, faxed, or delivered in person to the address below.

Mailing Address: Michelle Ramirez
Proposition 65 Implementation Program
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-12B
Sacramento, California 95812-4010

Fax: (916) 323-2265

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. By sending us your comments you are waiving any right to privacy you may have in the information you provide. Individual commenters should advise OEHHA when submitting documents to request redaction of home address or personal telephone numbers. Electronic files submitted should not have any form of encryption.

If you have any questions, please contact Michelle Ramirez at Michelle.Ramirez@oehha.ca.gov or at (916) 445-6900.

References

Food and Drug Administration (FDA, 2018). FDA approved drug label for AVASTIN® (bevacizumab), Reference ID: 4277004, revised June-2018. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s323lbl.pdf