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September 21, 1988

IDENTIFICATION OF CHEMICALS AS "KNOWN TO THE STATE TO CAUSE REPRODUCTIVE TOXICITY"

Recommendations of the Subpanel on Reproductive Toxicity
Safe Drinking Water and Toxic Enforcement Act of 1986
Scientific Advisory Panel

1. General Principles

A. The criteria included herein will be utilized by the Scientific Advisory Panel to identify chemicals to be recommended as known to the state to cause reproductive toxicity, for purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65").

B. These criteria are intended to give the Scientific Advisory Panel maximal flexibility in evaluating all pertinent scientific information in determining whether a chemical is known to the state to cause reproductive toxicity. These criteria are not intended to limit the scope of the Panel's consideration of appropriate scientific information.

C. These criteria should be updated periodically, as appropriate, to incorporate contemporary scientific views dealing with the evaluation of reproductive toxicity.

2. Definitions

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A. Chemicals known to the state to cause reproductive toxicity include those that have been clearly shown to ~~be toxic~~ adversely affect reproductive outcomes by "scientifically valid testing according to generally accepted principles" (Health and Safety Code, Section 25249.8(b)).

B. For purposes of these criteria, "reproductive toxicity" includes "developmental toxicity," "female reproductive toxicity," and "male reproductive toxicity."

C. "Developmental toxicity" means adverse effects on the product of conception (i.e., the conceptus), including, but not limited to:

(1) Embryo/fetal mortality (or miscarriage, spontaneous abortion, or stillbirth), malformations, structural abnormalities and variations, and altered fetal growth.

(2) Postnatal growth and development, including physiological deficits, and, where appropriate, neurological, neurobehavioral, and psychological deficits.

(3) Transplacental carcinogenesis.

D. "Female reproductive toxicity" means effects on the adult, or where appropriate, developing, female organism, including, but not limited to:

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(1) Adverse effects on gonadal gross or histological structure or function, including:

a. Genetic damage to the ovum or its precursors.

b. Alterations in ovulation, menstrual (estrous) cycle and/or menstrual disorders.

c. Impaired endocrine function (or endocrine toxicity).

(2) Impaired reproductive performance (e.g., subfertility or infertility), including:

a. Increased pregnancy wastage (e.g., miscarriage, spontaneous abortion, or stillbirth).

b. Inability (~~to conceive~~) or decreased ability (i.e., increased time) to conceive.

E. "Male reproductive toxicity" means effects on the adult, or, where appropriate, developing male organism, including, but not limited to:

(1) Adverse effects on gonadal gross or histological structure or function, including:

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a. Genetic damage to the spermatozoon or its precursors.

b. Impaired sperm and/or seminal fluid production, including alteration in sperm number, morphology, motility, and ability to fertilize.

c. Impaired endocrine function (or endocrine toxicity).

(2) Impaired reproductive performance (e.g., subfertility, infertility, or impotence).

3. Developmental effects shall meet at least one of the following criteria for recommendation as known to the state to cause reproductive toxicity.

A. Sufficient evidence in humans.

(1) Includes any of a variety of epidemiological studies, including a single well conducted study, so long as the evidence is scientifically valid according to generally accepted principles (e.g., accurate exposure and toxicity endpoint information, proper control of confounders, effect modifiers and other risk factors).

(2) Clinical cases are useful if carefully delineated with respect to the presence of a specific syndrome (or developmental toxicity endpoint) and if they consistently show an association

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between exposure to the agent and the occurrence of the toxic endpoint. Exposure to the agent should have occurred at the developmental stage relevant to the endpoints identified.

B. Limited evidence or suggestive evidence in humans, supported by sufficient experimental animal (mammalian) data, as described below.

C. Sufficient evidence in experimental animals (mammals), such that extrapolation to humans is appropriate. "Sufficient" animal data would, in most cases, be based on the adequacy of the following:

(1) The experimental design, including overall protocol and numbers of animals, and presence of appropriate controls.

(2) The exposure should be relevant to expected human exposures, in terms of route of exposure and in terms of timing, with regard to critical periods of development. While it is desirable to have the exposure reflect relevant human exposures, ~~often~~ practical considerations may lead to development of data under ~~protocol~~ constraints will necessitate other types of exposures. For example, the need to separate dam and litter during inhalation exposure may make oral exposure more appropriate.

(3) Numbers of dose levels, so that a dose-response relationship can be evaluated. It is desirable that the high dose level should elicit maternal/paternal toxicity, and the low dose should elicit no observable adverse effect for adult and offspring.

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(4) Consideration of maternal toxicity.

When developmental effects are produced only at maternally toxic doses, the types of developmental effects should be examined carefully ~~and not~~ discounted as being secondary to maternal toxicity. to determine whether they should be

(5) Number of tests or experimental animal species.

a. Data on a single species from a well conducted reproductive toxicity study may be sufficient to classify an agent as a reproductive toxicant.

b. Data on more than one species or from more than a single study increase the confidence for classification of an agent as a reproductive toxicant.

(6) Other considerations, including, but not limited to, metabolic and pharmacokinetic data which may ~~be~~ aid in evaluating the relevance of animal data to human exposures.

D. In evaluating the sufficiency of data, a "weight-of-evidence" approach shall be used to evaluate the body of information available for a given chemical.

4. Female reproductive effects will be evaluated by the following criteria for recommendation as known to the state to cause reproductive toxicity.

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(Reserved, pending the availability of EPA Guidelines).

5. Male reproductive effects will be evaluated by the following criteria for recommendation as known to the state to cause reproductive toxicity.

(Reserved, pending the availability of EPA Guidelines).

6. The determination of whether a chemical is to be recommended to be listed as known to the state to cause reproductive toxicity, the association between developmental toxicity or female or male reproductive toxicity and the toxic agent in question should make biologic sense. That is, based on known principles of reproductive and developmental biology, physiology, and toxicology, a sound scientific basis should exist for the observed adverse effects and the known characteristics of the particular toxic agent.

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