

(Nov. 1993) CRITERIA FOR RECOMMENDING CHEMICALS FOR LISTING AS "KNOWN TO THE STATE TO CAUSE REPRODUCTIVE TOXICITY"

1. General Principles

- A. The criteria included herein shall be utilized by the Office of Environmental Health Hazard Assessment Science Advisory Board Developmental and Reproductive Toxicant (DART) Identification Committee 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 shall be updated periodically, as appropriate, to incorporate contemporary scientific views dealing with the evaluation of reproductive toxicity.
- C. These criteria are intended to give the DART Identification Committee 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 Committee's consideration of appropriate scientific information, nor to limit its use of best scientific judgment.
- 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.

2. Definitions

- A. Chemicals known to the State to cause reproductive toxicity include those that have been clearly shown to be toxic 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" is defined to include adverse effects on the products of conception (i.e., the conceptus), including but not limited to:

- (1) Embryo/fetal mortality (including resorption, miscarriage/spontaneous abortion, or stillbirth), malformations, structural abnormalities and variations, altered fetal growth, and change in gestational age at delivery.
 - (2) Postnatal parameters including growth and development, physiological deficits and delay, neurological, neurobehavioral and psychological deficits, altered sex ratio, abnormal sexual development or function, and morbidity or mortality.
 - (3) Transplacental carcinogenesis.
 - (4) Somatic or genetic (germ cell) mutations in the conceptus.
- D. "Female reproductive toxicity" is defined to include effects on the adult or, where appropriate, developing female organism, including, but not limited to:
- (1) Adverse effects on reproductive structure or function including:
 - a. Genetic damage to the ovum or its precursors.
 - b. Alterations in ovulation, menstrual (estrous) cycle and/or menstrual (estrous) disorders.
 - c. Impaired or altered endocrine function.
 - d. Complication of pregnancy.
 - (2) Impaired reproductive performance (e.g., sub fertility or infertility, including):
 - a. Increased pregnancy wastage (e.g., miscarriage/spontaneous abortion or stillbirth).
 - b. Inability or decreased ability to conceive (e.g., time to conception).
 - c. Adverse effects observed in sexual behavior, onset of puberty, fertility, gestation, parturition, lactation, or premature reproductive senescence.

- E. "Male reproductive toxicity" is defined to include effects on the adult or, where appropriate, developing male organism, including, but not limited to:
 - (1) Adverse effects on reproductive structure or function including:
 - a. Genetic damage to the spermatozoon or its precursors.
 - b. Impaired sperm and/or seminal fluid production, including alterations in sperm number, morphology, motility, and ability to fertilize.
 - c. Impaired or altered endocrine function.
 - (2) Impaired reproductive performance (e.g., sub fertility, infertility, or impotence).
- 3. Developmental, and female and male reproductive 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, so long as the study or studies are scientifically valid according to generally accepted principles and provide convincing evidence to support a causal relationship between exposure to the chemical, and the developmental or reproductive effect in question. This requires accurate exposure and toxicity endpoint classification and proper control of confounding factors, bias, and effect modifiers.
 - (2) Clinical cases can be used if carefully delineated with respect to the presence of a specific syndrome (or developmental/reproductive toxicity endpoint) and if the reports consistently show an association between exposure to the agent and the occurrence of the particular endpoint of developmental or reproductive toxicity. Exposure to the agent should have occurred at the developmental or reproductive stage relevant to the endpoints identified.
 - (3) Weight of evidence considerations.

- a. Data from multiple studies increase the confidence for classification of an agent as a developmental or reproductive toxicant, and unless there is an exceptionally strong study (see below), effects should occur in more than one human study for a chemical to be recommended for listing on the basis of epidemiologic evidence alone.
 - b. Data from a single well conducted epidemiologic developmental or reproduction toxicity study showing a clear relationship between exposure and effect may be sufficient to classify an agent as a developmental or reproductive toxicant, provided there are not equally well conducted studies which do not show an effect and which have sufficient power to call into question the repeatability of the observation in the positive study.
- 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, in terms of route of administration, is relevant to expected human exposures, and in terms of timing, with regard to critical periods of development for developmental toxicity, sexual maturation, stage of pregnancy, or other critical periods for female reproductive toxicity, and sexual maturation, spermatogenesis, or other critical periods for male reproductive toxicity.
 - (3) Number of dose levels, so that the presence of a dose-response relationship can be evaluated. It is desirable that the high dose level should elicit maternal toxicity in developmental studies, and systemic toxicity in female and male reproductive studies, and that the low dose should elicit no observable adverse effect for adult and offspring.
 - (4) Consideration of maternal and systemic toxicity.

Differentiating between (a) the effects of a toxic agent on the conceptus or reproduction and (b) the effects on the conceptus or reproduction that are secondary to the maternal or systemic toxic effects is sometimes difficult and may require special attention, on a case by case basis.

- (5) Number of tests or experimental animal species.
 - a. In general, effects should occur in multiple studies or multiple species for a substance to be recommended for listing.
 - b. Weight of evidence considerations.
 1. Data on a single species from a well conducted developmental or reproduction study may be sufficient to classify an agent as a reproductive toxicant provided there are not equally well conducted studies which do not show an effect and which have sufficient power to call into questions the repeatability of the observation in the positive study.
 2. 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 those listed below, which can increase or decrease the confidence for classification of an agent as a reproductive toxicant.
 - a. Severity or consistency of findings.
 - b. Metabolic and pharmacokinetic data.
 - c. Time course of events.
4. Statistical considerations and biological plausibility.
 - A. Statistical analyses are important in determining the effect of a particular agent; however, the biological significance of the data should not be overlooked. Given the number of endpoints that can be quantified in developmental and reproduction studies, a few statistically significant

differences may occur by chance alone. Conversely, apparent dose-related trends may be biologically relevant even though statistical analyses do not indicate a significant effect.

- B. In determining whether a chemical is to be recommended to be listed as known to the State to cause reproductive toxicity, the biological plausibility of the association between the adverse reproductive effects observed and the chemical in question should be considered. Confidence is increased when, based on known principles of developmental and reproductive biology, physiology, and toxicology, a sound scientific basis exists for the observed adverse effects and the known characteristics of the particular chemical. Conversely, confidence is decreased if the observed adverse effects are contradictory to the known characteristics of the particular chemical.