GLOSSARY

Adverse effect: A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge.

Area Under the Curve (AUC): Area under the concentration versus time curve. The AUC is a summary measure that integrates serial assessments of a dose over the duration of the study.

Aryl hydrocarbon receptor (AhR): An intracellular protein that is a ligand-dependent transcription factor that functions in partnership with a second protein, the aryl hydrocarbon receptor nuclear translocator (Arnt).

Aryl hydrocarbon receptor nuclear translocator (Arnt): An intracellular protein that functions as a transcription factor in the cell in partnership with a second protein, the aryl hydrocarbon receptor (the AhR).

Background exposure: The exposure that regularly occurs to members of the general population from exposure media (food, air, soil, etc.) that have dioxin concentrations within the normal background range. Most (> 95%) of background exposure results from the presence of minute amounts of dioxin-like compounds in dietary fat, primarily from the commercial food supply. The origin of this background exposure is from three categories of sources: naturally formed dioxins, anthropogenic dioxins from contemporary sources, and dioxins from reservoir sources. The term "background exposure" as used in this document should not be interpreted as indicating the significance or acceptability of risk associated with such exposures.

Benchmark dose (BMD): A statistical lower confidence limit on the dose that produces a predetermined change in response rate of an adverse effect, typically 1–10%, compared to background.

Body burden: Body burden is defined as the concentration of TCDD and related chemicals in the body and is typically expressed as ng/kg body weight. In animals, these values are calculated from studies at or approaching steady-state and are associated with either biochemical or toxicological responses. In addition, these values are calculated on the basis of knowledge of the species-specific half-life and the exposure, or they are estimated on the basis of the TCDD tissue concentration, the size of the tissues, and the weight of the animal. In humans the values are typically presented as steady-state body burdens and are estimated on the basis of an intake rate and the half-life of TCDD in humans. Alternatively, body burdens in humans are estimated on the basis of lipid adjusted serum or adipose tissue TCDD or TEQ concentrations.

Cancer: A family of diseases affecting cell growth and differentiation, characterized by an abnormal, uncontrolled growth of cells.

Carcinogen: An agent capable of inducing cancer.

Carcinogenesis: The origin or production of a benign or malignant tumor. The carcinogenic event modifies the genome and/or other molecular control mechanisms of the target cells, giving rise to a population of altered cells.

Chronic effect: An effect that occurs as a result of repeated exposures over a long period of time in relation to the lifetime of the organism.

Chronic exposure: Multiple exposures occurring over an extended period of time or a significant fraction of the animal's or the individual's lifetime.

Chronic study: A toxicity study designed to measure the (toxic) effects of chronic exposure to a chemical.

Chronic toxicity: The capacity of a substance to cause adverse human health effects as a result of chronic exposure.

Cohort: A group of animals of the same species, including humans, that is identified by a common characteristic and that is studied over a period of time as part of a scientific or medical investigation.

Confidence interval (CI): A range of values for a variable of interest, for example, a rate, constructed so that this range has a specified probability of including the true value of the variable.

Confounder: A condition or variable that is both a risk factor for disease and is associated with an exposure of interest. This association between the exposure of interest and the confounder (a true risk factor for disease) may make it falsely appear that the exposure of interest is associated with disease.

Congeners: Compounds that have similar chemical structures or belong to closely related chemical families

Coplanar: Descriptive term referring to the fact that multi-ringed chemical structures can assume a flat configuration, with rings in the same spatial plane.

Dioxin-like: An adjective that describes compounds that have similar chemical structure and physical-chemical properties and invoke a common battery of toxic responses as does 2,3,7,8-TCDD. Because of their hydrophobic nature and resistance towards metabolism, these chemicals persist and bioaccumulate in fatty tissues of animals and humans. Certain members of the dioxin, furan, and PCB family are termed “dioxin-like” in this reassessment.

Effective dose (ED): The dose that corresponds to an increase, expressed as a percent response, in relation to expected levels of an adverse effect that can be defined as a percent increase over background rates or a percent increase between background and maximal rates.

Effective dose$_{01}$ (ED$_{01}$): The dose corresponding to a 1% increase in an adverse effect. Effective dose evaluation at the 10% response level (ED$_{10}$ or lower bound on ED$_{10}$ [LED$_{10}$]) is somewhat the norm, given the power of most chronic toxicology studies to detect an effect. In cases where the data allow evaluation at a lower effective dose level, the Agency suggests using the lower value. Such is the case for 2,3,7,8-TCDD.

Epidermal growth factor (EGF): A mitogenic polypeptide active on a variety of cell types, especially, but not exclusively, epithelial.

Follicle stimulating hormone (FSH): FSH is an acidic glycoprotein secreted by the anterior pituitary gland. In women, follicle stimulating hormone stimulates the development of ovarian follicles (eggs) and stimulates the release of estrogens. In men, follicle stimulating hormone stimulates the production of sperm.

Half-life: A measure of the time required to reduce to one-half the original concentration of a specified chemical in the body.

Hormone: Control chemicals produced by tissues or organs specialized for that function and that exert their highly specific effects on other tissues of the body.

Latency Period: The time between first exposure to an agent and manifestation or detection of a health effect of interest.

Ligand: Any molecule that binds to another. In normal usage, a soluble molecule such as a hormone or neurotransmitter that binds to a receptor, usually with high affinity.

Lower limit on effective dose$_{01}$ (LED$_{01}$): The 95% lower confidence limit of the dose of a chemical needed to produce a 1% increase of an adverse effect in those exposed to the chemical or to 1% of the maximal response relative to control.

Lowest-observed adverse effect level (LOAEL): The lowest exposure level at which there are statistically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

Luteinizing hormone (LH): A hormone that acts with the follicle stimulating hormone (FSH) to stimulate sex hormone release.

Margin of exposure (MOE): The LED$_{10}$, LED$_{01}$, or other point of departure divided by the actual or projected environmental exposure/dose of interest, expressed as a ratio.

Minimal risk level (MRL): An estimate of daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

No-observed-adverse effect level (NOAEL): The highest exposure level at which there are no statistically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or to be precursors to adverse effects.

No-observed-effect level (NOEL): An exposure level at which there are no statistically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control.

Pharmacokinetics: The quantitative description of the process of chemical disposition: absorption, distribution, metabolism, and excretion (metabolism and excretion equal elimination).

Physiologically based pharmacokinetic (PBPK) model: Physiologically based model used to characterize pharmacokinetic behavior of a chemical. Available data on blood flow rates and metabolic and other processes that the chemical undergoes within each compartment are used to construct a mass-balance framework for the PBPK model.

Point of departure (POD): The dose-response point that marks the lower end of the range of observation and the beginning of a low-dose extrapolation. This point is most often the upper bound on an observed incidence or on an estimated incidence from a dose-response model or the lower bound on the dose associated with such an incidence.

Promoter: An agent that is not carcinogenic itself but that when administered after an initiator of carcinogenesis stimulates the clonal expansion of the initiated cell to produce a neoplasm.

Receptor: A molecular structure within a cell or on the cell's surface that is characterized by selective binding of a specific substance and a specific physiologic effect that accompanies the binding (for example, see aryl hydrocarbon receptor).

Receptor site: The portion of the receptor molecule or structure with which the compound (ligand) interacts.

Reference dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, a LOAEL, or a benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments.

Relative potency (REP): The ratio of the potency of the congener to the standard toxicant in that specific study; a concept similar to toxic equivalency but based on a single study, species, or matrix, etc., and not averaged to obtain a general toxic equivalency value.

Relative risk (RR): The relative measure of the difference in risk between the exposed and unexposed populations in a cohort study. The relative risk is defined as the rate of disease among the exposed divided by the rate of the disease among the unexposed. A relative risk of 2 means that the exposed group has twice the disease risk as the unexposed group.

Reservoir sources: Reservoirs are materials or places that contain previously formed CDD/CDFs or dioxin-like PCBs and have the potential for redistribution and circulation of these compounds into the environment. Potential reservoirs include soils, sediments, biota, water, and some anthropogenic materials. Reservoirs become sources when they have releases to the circulating environment.

Risk (in the context of human health): The probability of injury, disease, or death from exposure to a chemical agent or a mixture of chemicals. In quantitative terms, risk is expressed in values ranging from zero (representing the certainty that harm will not occur) to one (representing the certainty that harm will occur).

Slope factor: An upper bound, generally approximating or exceeding a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per mg/kg/day, is generally reserved for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100.

Standardized mortality ratio (SMR): This is the relative measure of the difference in risk between the exposed and unexposed populations in a cohort study. The SMR is similar to the relative risk in both definition and interpretation. This measure is usually standardized to control for any differences in age, sex, and/or race between the exposed and the reference populations. It is frequently converted to a percent by multiplying the ratio by 100.

Statistical significance: The probability that a result may be due to chance alone. By convention, a difference between two groups is usually considered statistically significant if chance could explain it only 5% of the time or less. Study design considerations may influence the a priori choice of a different statistical significance level.

Thyroid stimulating hormone (TSH): A hormone secreted by the anterior pituitary gland that activates certain actions in thyroid cells leading to production and release of the thyroid hormones (T3 and T4). T3 and T4 blood levels feed back on the hypothalmus/pituitary gland and decrease TSH production when T3 and T4 levels are high.

Tolerable daily intake (TDI): A TDI is an estimate of the amount of a contaminant in food or drinking water that can be ingested daily over a lifetime without a significant health risk. The term is used frequently in World Health Organization (WHO) health assessments. The

term "tolerable" is used, as contaminants do not serve an intended function and as intake is unavoidably associated with the basic consumption of food and water. Tolerable does not generally connote "acceptable" or "risk free."

Toxic equivalence (TEQ): The toxic equivalency factor (TEF) of each dioxin-like compound present in a mixture multiplied by the respective mass concentration. The products are summed to represent the 2,3,7,8-TCDD toxic equivalence of the mixture.

Toxic equivalency factor (TEF): TEFs compare the potential toxicity of each dioxin-like compound present in a mixture to the well-studied and well-understood toxicity of 2,3,7,8-TCDD, the most toxic member of the group, with the TEF of 2,3,7,8-TCDD being 1. TEFs are the result of expert scientific judgment using all of the available data and taking into account uncertainties in the available data.

Transcription: The process of constructing a messenger RNA molecule using a DNA molecule as a template, with resulting transfer of genetic information to the messenger RNA.

Transcription factor: A substance, usually a protein, that is developed within the organism and that is effective in the initiation, stimulation, or termination of the genetic transcription process.

Upper bound: A plausible upper limit to the true value of a quantity or response. This is usually not a true statistical confidence limit.

Weight-of-evidence: An approach used for characterizing the extent to which the available data, including human, animal, and mechanism of action, support the hypothesis that an agent causes an adverse effect, such as cancer, in humans. The approach considers all scientific information, both positive and negative, in determining whether and under what conditions an agent may cause disease in humans.