Multiple Stressor and Chemical Mixtures Glossary*

Additive (Greater or less than): Examples of additive models include concentration addition, toxic equivalency factors, effect summation and independent action (Stanton 2012); additive = if effects are as predicted; synergistic = more than additive effects, antagonistic = less than additive effects (Norwood et al. 2003).

Adverse response: a harmful and undesired effect resulting from an intervention ("Glossary" AHRQ).

Agent (vs. Stressor): stressor: anything that increases mortality rate in a population, stressor is any physical, chemical, or biological entity that can induce an adverse response ("Glossary" EPA); agent: an active and efficient cause; capable of producing a certain effect; It is considered to be more neutral than stressor ("Glossary" EPA).

Allostatic load: cumulative effects of adaptive processes (usually from acute stress); physiological consequences of chronic exposure to fluctuating or heightened neural or neuroendocrine response that results from repeated or chronic stress (McEwan and Stellar 1993).

Bioavailability: The proportion of a drug or other substance that enters the circulation when introduced into the body and so is able to have an active effect (Merriam-Webster).

Bliss model (vs. Loewe vs. Carter model): assumes stressors act at different sites and independently of one another and estimates the combined effect of two stressors as the product of the probability of effect of each stressor individually (Bliss 1939).

Carter Model (vs. Bliss vs. Loewe models): numerical algorithm used in mortality forecasting and life expectancy forecasting. The input to the model is a matrix of age specific mortality rates ordered monotonically by time, usually with ages in columns and years in rows. The output is another forecasted matrix of mortality rates (Lee 1992; Lee and Cater 2000).

Chemical mixtures (vs. multiple stressors): two or more substances which have been combined such that each substance retains its own chemical identity; multiple stressor: combination of chemical, biological and physical agents (Lokke 2009).

Co-exposures : simultaneous exposure to two or more agents.

Collinearity: Collinearity is a situation where there is close to a near perfect linear relationship among some or all of the independent variables in a regression model (Brannan et al. 1998).

Combined exposure vs. mixture vs. co-exposure: combined exposure and co-exposure are same thing (Hennes et al. 2012).

Concentration addition: Concentration addition is, in theory, expected to successfully describe chemical interactions if two or more chemicals cause toxicity by acting on the same molecular site within the organism. The strength of binding of each chemical to the site of toxic action need not be the same, but the effects of the bound chemicals should be additive (Borgmann et al. 2008); Concentration addition is limited in that it cannot be applied to effect levels greater than the maximal effect achieved by the least efficacious compound included in the mixture (Silva et al. 2002). Therefore, this model cannot appropriately assess the effect of mixtures containing a partial agonist (i.e., an agonist with less than maximal efficacy) (Howard et al., 2010). For metals, if the site of toxic action is on the surface of the organism, if this is the same as the site of chemical interaction for bioaccumulation, if there is only one such site, and if metal bioaccumulation interactions are purely competitive (Borgmann et al. 2008).

Cumulative risk assessment: involves the consideration of the aggregate ecologic or human health risk to the target entity caused by the accumulation of risk from multiple stressors ("Glossary" EPA).

CVOC's: chlorinated solvents; chlorinated volatile organic compounds.

DNAPL's: Dense non-aqueous phase liquids.

Dose addition (vs Response Addition): predicted mixture response based on ED50 dose (assumes common mechanisms of action). Response addition: summing the probabilistic risks of an adverse effect for the mixture components (Teuschler 2007).

Dredging residual: portion of contaminant that is not removed but remobilized during dredging.

Effect Summation (Response Addition): summing the actual biological measurements of the adverse effect for the mixture components (Teuschler 2007).

Environment-wide Association Study (EWAS): epidemiological data are comprehensively and systematically interpreted in a manner analogous to a Genome Wide Association Study; high thoroughput analysis methods (Patel et al. 2010).

Epigenetics: the study of inherited changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence (Bird 2007).

Exposome (vs. Responseome): exposome: encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards, environmental equivalent of genome (Wild 2005); see also: http://www.cdc.gov/niosh/topics/exposome/.

Exposure assessment: branch of environmental science that focuses on the processes that take place at the interface between the environment containing the contaminant(s) of

interest and the organism(s) being considered; tries to measure how much of a contaminant can be absorbed by an exposed target organism, in what form, at what rate and how much of the absorbed amount is actually available to produce a biological effect (Exposure Factors Handbook).

Generalized Concentration Addition: generalization of concentration addition that describes the additive combinatorial effects of full agonists, partial agonists, and competitive antagonists (Howard and Webster 2009). GCA provides a definition of non-interaction that encompasses combinations with linear isoboles of any slope (Howard et al., 2010).

GLM: General linear models (e.g. linear regression, analysis of variance); modifies the Least Squares method and defines variance in each point rather than assuming variance is equal at all points (McCullagh and Nelder 1989).

Hazard Assessment: does not distinguish between different modes of action; first step in risk assessment, identifies risks ("Electronic Code").

High throughput screening: allows a researcher to quickly conduct thousands of chemical, genetic or pharmacological tests understanding the interaction or role of a particular biochemical process in biology (Staff 2008).

Hill Equation: describes the fraction of the macromolecule saturated by ligand as a function of the ligand concentration; it is used in determining the degree of cooperativeness of the ligand binding to the enzyme or receptor (Hill 1910).

Independent action: an additive model in which each toxicant produces an effect independent of the other and by a different mode of action (Newman and Unger 2003).

Integrated addition: like-acting chemicals are assigned to a common grouping (Olmstead and LeBlanc 2005).

Interaction (vs. non-interactions): greater-than-additive effects by mixtures of toxicants (Norwood et al. 2003).

In vivo vs. in vitro approaches: in vivo=experimenting in the whole living organism aka "within the living;" in vitro=in test tube/controlled experiment aka "within the glass" (Lipinski 2004).

Isobologram: constructed on a coordinate system composed of the individual drug doses, commonly contains a straight "line of additivity" that is employed to distinguish additive from synergistic and antagonistic interactions (Tallarida 2006); isoboles join doses of equal activity.

Level of Detection (vs. background): the lowest quantity of a substance that can be distinguished from the absence of that substance (a blank value) within a stated confidence limit (MacDougall and Crummett 1980).

Linear models (vs. Threshold models): linear model: regression model, no limit; threshold model: a threshold value, or set of threshold values, is used to distinguish ranges of values where the behavior predicted by the model differs in some important way. A particularly important instance arises in toxicology, where the model for the effect of a drug may be that there is zero effect for a dose below a critical or threshold value (Priestley 1988).

Loewe Model (vs. Bliss model, vs. Carter model): assumes that combined stressors affect the same site and do not act independently (Loewe and Muischnek 1926).

Maximum cumulative ratio approach: the ratio of the cumulative toxicity received by an individual from exposure to multiple chemical stressors to the largest toxicity from a single chemical stressor. The MCR is a quantitative measure of the difference in an individual's toxicity estimated using a chemical-by-chemical approach and using an additive model of toxicity (Price and Han 2011).

Mixtures (vs combined exposures): traditional idea of mixtures (i.e. exposures to multiple contaminants) and the broadened idea of mixtures (i.e. exposure to a toxicant and a stressor) (Stanton 2012).

Mixture toxicity assessment: characterize effects of individual chemicals and use data from single chemical exposures to predict mixture effects; compare mixture model predictions to experimental (observed) results.

NOAELs: No observed adverse effect level.

Non-interaction: additivity; no interaction between poisons in a mixture (Norwood et al. 2003).

Partial agonist: chemicals that bind to and activate a given receptor, but have only partial efficacy at the receptor relative to a full agonist (Williams and Calvey 2001).

PCR factor analysis: estimates factors that represent groups of highly correlated components (Dodge 2003).

Performance Reference compound: standards used to determine rates of passive absorption.

Phenotypic anchoring: the linkage of specific patterns of gene expression to conventional parameters of toxicity or adverse effects (Tennant 2005).

Phthalates: "plasticizers," group of industrial chemicals known to cause endocrine system disruptions ("Phthalates").

Phthalate syndrome: cryptorchidism, hypospadias, atrophy or agenesis of sex accessory organs, testicular injury, reduced daily sperm production, delayed preputial separation, decreased (feminized) anogenital distance (AGD) (Foster 2006).

Random Forest analysis: Repeats tree procedure over and over; bootstrap procedure to randomly sample from original dataset without having to decide how far down the tree to go. Data gets mixed up for each constituent concentration.

REACH: European equivalent of TSCA on a compound by compound approach.

Redundancy: the inclusion of extra components that are not strictly necessary to functioning, in case of failure in other components; many species are redundant and their loss will not influence the community function as long as crucial species populations are maintained (Newman and Unger 2003).

Regularization: a variable selection method that contains influence of each regression coefficient; shrinks them back to zero. Identifies which variables are most important.

Regression Trees: look at importance of different constituents but not all the interactions; creates step functions. Graphical depictions look like cladogram; classification of sample according to binary splits in exposure.

Relative potency factor: used to weigh a biological response to related chemicals in terms of a single "index chemical". For example: REPs are used to compare cytochrome P450 1A1 induction by polychlorinated biphenyls to that by TCDD Peters 2006).

Resilience: in ecology, it is one possible ecosystem response to a perturbation or disturbance. A resilient ecosystem resists damage and recovers quickly from stochastic disturbances (Merriam-Webster).

Responseome: overall effect of multifaceted exposures that can be defined by genomics, epigenomics, proteomics, metabolomics, and transcriptomics.

Response addition (vs. Dose addition): non-similar mode of action based on probability theory (cannot use ED50); one of main mixture models, differing potencies of each of the mixture constituents is not important since the effect of each toxic constituent's concentration in the mixture is combined in the prediction of the mixture toxicity (Norwood et al. 2003); If all metals in a mixture have different sites of toxic action, then one might expect their effects to be independent and toxicity of the metal mixture could be predicted using response addition (Borgmann et al. 2008); summing the probabilistic risks of an adverse effect for the mixture components (Teuschler 2007).

Risk difference additivity: independent action implies risk difference additivity but additivity does not imply independent action; risk difference additivity is not a natural relation between effects that occur; additivity is simply a statistical null hypothesis, which, under certain conditions, can be derived from the biologic null of independent action (Rothman and Greenland 1998).

Site action (vs mechanism of action): site of exposure (Skinner and Guerrero-Bosagna 2009); mechanism of action: the specific biochemical interaction through which a drug substance produces its pharmacological effect. A mechanism of action usually includes mention of the specific molecular targets to which the drug binds, such as an enzyme or receptor (Merriam-Webster).

Stressor: anything that increases mortality rate in a population; anything that alters ecosystem and human health in a negative way ("Glossary" EPA); a response to anything that threatens homeostasis (Moberg and Mench 2000); anything that reduces fitness.

Sufficient similarity: two mixtures close in chemical composition where there are small differences in their components and in the proportions of their components ("Glossary" EPA).

Target signaling pathway approach: assumes common signaling pathway but not same mechanism of actions.

TERESA: Toxicological evaluation of source aerosols; study of coal fired power plant emissions.

Threshold models (vs. linear models) theory: assumes no response below a certain low dose.

Toxic Equivalency Factor (TEF): an empirically derived factor that scales the toxicity of a chemical (e.g. dioxin, or dioxin-like PCB, compounds that have toxic modes of action involving binding to aryl hydrocarbon receptor to that of TCDD) (Newman and Unger 2003).

Toxic interaction: significant deviation from a "no-interaction" or "additive" expectation.

Vapor intrusion: a process by which chemicals in soil or groundwater migrate to indoor air above a contaminated site ("Glossary" EPA).

Vulnerability: susceptibility to irreversible damage by toxicants (Newman and Unger 2003).

Weight of Evidence approach to interactions: whether a reasonable person reviewing the available information could agree that the conclusion was plausible (Newman and Unger 2003).

Whole mixtures approaches (vs. component based approaches): whole mixture approach: direct toxicity testing of the mixture; vs. component based approach: estimating the total toxicity from information on identified components only (Kortenkamp et al., 2009).

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