Appendix 4 - Layered Conservatism Embedded in Risk Assessment Practice

In outlining principles for regulatory analysis in EO 12866 and the Information Quality Guidelines, OMB has stated that risk assessment should be an "objective, realistic, and scientifically balanced analysis." All EPA risk assessments generally fail to meet these principles. Below is a list of procedures, assumptions, and practices routinely employed in EPA risk assessments that run counter to the principles that OMB has enumerated. Some of these are explicit default assumptions found in EPA risk assessment guidelines, and others are not verbatim policy defaults in guidelines but are EPA practice in these areas. In two areas, under cancer and non-cancer risk assessment, EPA has used new safety factors for some chemicals. These have not yet been formally identified in EPA guidelines. The list is not intended to be all-inclusive, nor is it intended to indicate that each assumption is used in every risk assessment.

Risk Assessment Components	Illustrations of Conservative Assumptions
Hazard Assessment	• Toxicity studies must demonstrate toxicity in animals at high doses to be predictive; Studies that show absence of effects at low doses are not predictive
	• Effects observed following high doses, as used in animal studies, are predictive of animal and human toxicity at low doses
	• The most sensitive animal species is presumed to be predictive for human toxicity
	• Positive animal studies are taken as predictive, whereas non-positive studies are taken as non-predictive; negative study results are presumed to be evidence of confounding and/or incorrect choice of animal model
	• Any effect observed in one study, irrespective of its quality of the study or results, is presumed to outweigh multiple non-positive or negative studies
	• Positive results from poorly run, non-GLP compliant studies, or from non-validated methods are presumed to outweigh negative studies from well-run studies and from well-validated methods; Highly positive results in poorly run studies are presumed to outweigh weakly positive results in well-conducted studies
	• Agents that cause toxicity by one route of exposure are presumed to do so by other routes of exposure. "Substantial" (undefined) contrary evidence is required to override this assumption
	• Agents are absorbed, distributed, metabolized and excreted in a similar manner in animals and humans
	• Target organ concordance (tumors site, specific fetal effects) is not a prerequisite for assessing whether positive animal results indicate human hazards; Lack of target organ concordance or specific effects in other strains, species or humans does not support the absence of an effect
	• Benign (histologically non-malignant) tumors are presumed to have potential to progress to malignant tumors and are counted as if they were malignant
	• Any change that is caused by an agent is presumed to be a toxic manifestation, and / or on the "critical path" to toxicity [“key events”] ; In virtually no case is any "measurable effect" considered to be adaptive, non-adverse or beneficial
	• In most cases, chemicals are presumed to be completely absorbed; Active compounds are not detoxified; Inactive compounds are completely metabolized to active compounds
	• Positive occupational and epidemiological studies provide evidentiary support for the existence of hazard; non-positive studies do not support the absence of an effect; negative studies are presumed evidence of confounding, low statistical power and/or model mis-selections (e.g. "healthy worker effect")
Exposure Assessment	• Exposed individuals are located at maximum exposure concentration (100% of the time)
	• Maximum concentration in any location are applies as continuous exposure everywhere (24 hour/day, 7 days/week), whether in air, water, food, or waste

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	• Individuals live in same location for 350 days / year for 70 years, or in some cases, 85 years (e.g. Butadiene)
	• Individual breathes 20 cubic meters (m^3) of air / day, 100% of which is presumed to be the most contaminated air
	• Workers stay with the same employer at the same location in the same job (if risky) for 45 years
	• Exposed individuals drink 2 liters of unprocessed tap water / day, 100% of which is presumed to be the most contaminated water
	• Exposed children eat 200 mg of environmental dirt / day, 100% of which is presumed to be the most contaminated soil
	• People consume 115 g fish / day
	• "High end" exposure scenarios (>=95 or 99.9 percentile) are used to represent the entire distribution
	• Use of patterns or label instructions are not relevant for setting exposures; Assume that higher exposure conditions are achieved (e.g. no ventilation when using product indoors)
	• Exposure is not affected by chemicals degrading in environment, partitioning to other media or environmental "sinks" (soil, carpets, etc.), or air exchanges in environment
	• Models for fate & transport, exposure assessment for each media or cumulative assessment use most sensitive soil type, combined with the lowest rates of degradation, air exchange, or water dispersion; 100% of mass used in each scenario
	• Unrealistic exposure scenarios used in some models (e.g., trespassing subsistence infants for waste sites)
	• Most susceptible / sensitive species, strain, sex, age, etc. are selected for the dose response assessment
Dose-Response Assessment	• The assumption is that an extrapolation is being performed from an "average" rodent to the "most sensitive" human, yet rodent studies selected for dose-response extrapolation are the "most sensitive" observation available.
	• Occupational epidemiology cohorts are assumed to have little/no diversity with regard to genetics and susceptibility.
	• The lowest adverse effect level (LOAEL) or no-adverse effect level (NOAEL) is selected for extrapolation
	• Maximum exposure is presumed to be the delivered dose; 100% of the absorbed dose is completely delivered to the critical target / organ
	• No repair mechanisms or surveillance processes are operative
	• Toxicity associated with the 'maximum tolerated dose' does not affect the potency estimate
	• Assumption of "linearity" (one molecule increases risk) for genotoxic carcinogens, and for nongenotoxic compounds (e.g., TCE) whenever "appropriate" (undefined)
	• A high dose of an agent for a short period of time is equivalent to a low dose spread over a lifetime (e.g. uncritical adherence to Haber's Law)
	• Delivered doses to lab animals are converted to estimated equivalent human doses by adjusting body weight to the 0.75 power; Children's doses are estimated by adjusting body weight to the 0.75 power, plus the additional safety factor for a child's putatively increased exposure due to increased breathing rate
	• The toxicity of a chemical mixture is presumed to be equal to the sum of the toxicity of each individual chemical, regardless of the toxicity type, competition or antagonism among chemicals
	• Results of studies in human volunteers are disregarded as irrelevant or dismissed as having been unethically obtained, regardless of the quality and utility of the data

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	• After the above steps are completed the following steps are completed for **non-cancer assessment** (reference doses or concentrations): ➢ The lowest observed adverse effect level (LOAEL) or no-adverse effect level (NOAEL) is selected as a starting point. This number is divided by the following: ➢ A 10-fold safety factor that presumes that humans are more sensitive than the most sensitive animals ➢ A 10-fold safety factor is used to account for potential difference in human sensitivity ➢ A 10-fold safety factor is used if a LOAEL is the starting point ➢ If a benchmark dose is used (e.g. 10% response level, BMD_{10}) for any effect, this level is divided by a 10-fold effect level extrapolation factor ➢ A 3-10-factor used if a full database is not available ("full" database is not defined) ➢ A combination of the following safety factors are then employed - A 3 to 10-fold safety factor if a subchronic study is used as the starting point; A 3-10 modifying factor; A 3-10 fold "other" adjustment factor for 'risk reduction' (e.g. adjusting timeline for reproductive studies, MEK, Butadiene) or 'severity of effect' (e.g. Thiram), or 'duration' factors (Perchlorate) ➢ 10-fold safety factor for subpopulations presumed but not demonstrated to be more sensitive than the most sensitive animal (FQPA)
	• The following steps are completed for **cancer assessment** (cancer potency / slope factors): ➢ Events that are on the "critical path" to toxicity [key events, receptor binding, general liver effects, foci] are used as the starting point for extrapolation ➢ Upper bound estimate of potency are used (e.g. 95% upper confidence limits) for both linear and non-linear models, often even when human data are used to calculate potency, e.g., butadiene (maximum likelihood estimate is more appropriate for human data) ➢ Linear extrapolation is used when the agent is mutagenic or acts through another mode of action "expected" to be linear at low doses (not defined), or human exposure or body burden is "high: (undefined) and "near" (undefined) doses associated with key events ➢ Linear extrapolation is also used as a default option when the data do not establish the mode of action; "Significant" data (undefined) needed to establish a mode of action ➢ Nonlinear extrapolation may be used when there is no evidence of linearity, and there is sufficient information to support a mode of action that is nonlinear at low doses. ➢ A chemical's mode of action is presumed to be different in children than adults thus linear extrapolations are used for children or other sensitive subpopulations (undefined); "Substantial" evidence (undefined) is required to override this assumption ➢ Once unit risk levels are derived, they may be divided by additional safety factors to account for 'sensitive subpopulations' or if other potential tumors can not be ruled out (e.g. gender factor applied for females for Butadiene) ➢ Assumption that all exposure from birth to age 70 is relevant in calculating lifetime cancer risk, rather than limiting exposures to biologically relevant age periods (exposures in later life stages, i.e., ages 50, 60, 70, are highly unlikely to have any impact on lifetime cancer risk).
Risk Characterization	• There are always susceptible subpopulations 'at risk'; Evidence for this conclusion is not presented for an individual chemical
	• Susceptible individuals are among the maximally-exposed members of the target population
	• No mitigating measures occur to affect exposure or dose for an entire lifetime

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	• Adverse effects are defined any "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." ➢ No evidence/counter evidence that all changes are 'adverse' ➢ Many unclear terms ['biochemical changes', 'impairment', 'reduces ability to respond'] ➢ Implies that exposures universally below a fixed threshold are per se adverse because they consume portion of the MOE/MOS
	• Reference doses or concentrations (RfDs or RfCs) defined as "an estimate (with uncertainty perhaps spanning an order of magnitude) of a daily exposure to the human population (including sensitive subpopulations) that is likely to be without appreciable risk of deleterious effects over a lifetime" ➢ No evidence that uncertainty in fact spans just one order of magnitude, contrary evidence ignored because it does not fit the definition ➢ Many unclear terms ["perhaps an order of magnitude", "order of magnitude" on left, right or split in half, "appreciable risk", or "deleterious effects"] ➢ An infinite number of values satisfy the definition, location on spectrum of qualifying values is not reported, highest value that satisfies the definition is the only value of interest, and is implied but not supplied
	• Cancer risks are described as "upper-bound excess lifetime risks estimated to result from continuous exposure to an agent at a concentration" that an absolute risk level (e.g. 1 x 10^{-6} risk from a concentration in 1 ug/L water), but the true risk "could be as low as zero" ➢ Many unclear terms: "could be as low as zero"; "upper bounds" (defined as a plausible upper limit to the true value of a quantity, but is usually not a true statistical confidence limit) ➢ Added safety factors intended to account for the fact that small increases in cancer risk at other locations / sites cannot be ruled out"; Inconsistent with statements that risk levels are "protective for humans (including sensitive subpopulations)"