Beyond Science and Decisions: From Problem Formulation to Dose-Response Assessment: Summary of Case Study: *The Human Relevant Potency Threshold:*

1. Summary of the Method Illustrated by the Case Study

The Human-Relevant Potency-Threshold (HRPT) method provides a means for determining the dose levels at which it is justifiable, and yet still conservative, to assume the dose addition model of combined action for assessing risks of exposure to chemical mixtures. The HRPT method employs actual human data to make this determination. Recognizing that human data are unavailable for the vast majority of chemicals to which humans may be exposed from the environment, the HRPT method uses data on human pharmaceuticals or endogenous effectors (hormones, neurotransmitters, etc.) to determine the Human-Relevant Potency-Threshold. These thresholds are then applied to other chemicals based on similarities in the mode of action or overt adverse outcome. Below these potency thresholds, the method provides justification for assuming the independent action model of combined action.

The HRPT approach also explicitly assumes, as a screening-level assessment tool, the Dose Addition - Common Adverse Outcomes (DA-CAOS) approach to cumulative risk assessment proposed by the National Research Council (2008), which was recently used in published risk assessments for chemicals with anti-androgenic potential, including phthalate esters (Kortenkamp & Faust, 2010; Benson 2009). The HRPT approach then builds upon that work to produce a second-tier analysis that calibrates application of the DA-CAOS approach based on potency and effect data for relevant human pharmaceuticals. In doing so, it combines the tenable assumptions of the DA-CAOS approach and empirical data used by Kortenkamp & Faust (2010) with the biologically based inclusion criteria of the Toxic Equivalency (TEQ) approach (Safe 1990), and calibrates these using empirical data on chemical potency from relevant human pharmaceuticals.

Using comparisons of human versus test-species sensitivity, potency differences between chemicals, and concentrations at which DA adverse effects are demonstrable in test species, the HRPT approach estimates the potency threshold at which DA would be a conservative, but tenable, assumption for humans. The steps involved are:

1. Defining the common adverse outcome or target organ effect upon which the cumulative effect from a group of chemicals is to be based. In most instances, this will be defined based on animal toxicology studies, but care should be taken to avoid effects that are arguably species specific and of questionable relevance to humans. It is important that

the effect is defined specifically and that constellations of effects be avoided unless clearly and definitively related by physiological and mechanistic understanding.

2. Identifying the chemicals known to produce the common adverse outcome in the test species and determining whether data indicate DA combined effects of those chemicals. If demonstrable, identify the lowest concentrations in mixtures at which DA occurs.

3. Defining, if possible, the modes of action that can lead to the adverse outcome in the test species.

4. Identifying chemicals, including drugs, known to produce the adverse outcome in humans, including among these, chemicals or drugs known to operate by relevant modes of action that can produce the adverse outcome.

5. Identifying chemicals for which the TEQ concept is justified based on satisfying TEQ requirements (see Table 1 in Borgert et al., 2012).

6. Gathering and comparing dose-response data for the chemicals and drugs of interest in humans and the test species, whether based on end-organ toxic effects or intermediate, obligate steps in the production of toxicity. (Examples are found in the Case Study - Borgert et al. 2012 - the former is exemplified by the comparison of the DES doses at which male reproductive tract malformations occur in humans versus rats; the latter, the comparisons based on doses of finasteride. Fortunately, because data providing direct dose sensitivity comparisons for frank adverse effects are rare, such as those for DES, comparisons based on measures of pharmacological effects will often be required.)

7. Based on the comparisons of human versus test species sensitivity, potency differences between chemicals, and concentrations at which DA adverse effects are demonstrable in test species, estimating the potency differential between species, and thus the potency threshold at which DA would be a conservative but tenable assumption for humans. Defining these potency thresholds is required for TEQ-compliant chemicals as well as for broader groups based only on common adverse outcome or intermediate steps in toxicity.

Section 4 of the Case Study (Borgert et al. 2012) describes application of the HRPT approach to phthalates and other chemicals with anti-androgenic potential in humans based on comparisons to human data for the pharmaceuticals diethylstilbestrol (DES) and finasteride. From the steps described therein, it proposes an effect-based application of DA to chemicals capable of producing CAOS whenever humans are exposed to concentrations of those chemicals greater than one-fifth the rat NOAEL/LOAEL for effects on the developing male reproductive tract. It proposes a potency-based application of DA to chemicals that specifically

inhibit 5α-reductase whenever the potency of the chemical is within one-tenth the potency of the human pharmaceutical finasteride.

The analysis presented in Section 2 of the case study (Borgert et al. 2012) show that calibrating the application of DA in this manner imparts at least an order of magnitude conservatism to the human risk assessment of chemicals with anti-androgenic potential. From those analyses, independent action (IA) is recommended as the most appropriate mixture model for human exposures to mixtures of potential anti-androgenic chemicals at concentrations lower than the derived HRPTs.

2. Problem Addressed by the Method

The 2008 National Research Council report "Phthalates and Cumulative Risk Assessment: Tasks Ahead," (NRC 2008) asserted that the underlying premises of TEQ-like approaches - e.g., chemicals are true congeners; are metabolized and detoxified similarly; produce the same biological effects by the same mode of action; exhibit parallel dose response curves - may be too restrictive and produce insufficiently conservative cumulative risk assessments. The NRC asserted that instead, dose addition (DA) should be applied to all chemicals that produce "common adverse outcomes" (CAOS) irrespective of their mode of action. Following this lead, a risk assessment was published for 15 anti-androgenic chemicals based on the DA-CAOS method (Kortenkamp & Faust 2010; Benson 2009). Ignoring the TEQ premises, however, contravenes pharmacological principles of receptor- and enzyme-mediated biological effects and dose-response analysis, and thereby undermines confidence in the extrapolation of DA from tested to untested doses.

Phthalate esters are a class of chemicals used in a wide variety of consumer products, including cosmetics, personal-care products, pharmaceuticals, medical devices, children's toys, food packaging, cleaning products and building materials. Humans are thus exposed to a variety of phthalate esters. Health concerns have been raised by studies in laboratory rodents showing anti-androgenic effects of some phthalate esters and other chemicals such as pesticides, alone and in mixtures, on the developing male reproductive tract. Published mixtures data and the human health risk assessment for phthalates and other potential anti-androgens were evaluated to determine how firmly the DA-CAOS concept is supported and with what level of statistical certainty the results may be extrapolated to lower doses in humans. Underlying assumptions of the DA-CAOS approach were tested for accuracy and consistency against data for two human pharmaceuticals and its logical predictions were compared to human clinical and epidemiological experience. Those analyses revealed an

unacceptably high level of uncertainty, rendering the DA-CAOS approach scientifically untenable for cumulative risk assessment beyond use as a coarse-level screening tool.

Therefore, the HRPT approach was developed as a more biologically based, advanced tier for cumulative risk assessment. This assessment structure is generally consistent with the tiered framework for cumulative risk assessment recommended by the IPCS (2011). The HRPT approach specifically accommodates both the DA-CAOS concept, where tenable, and the well-established TEQ method, but improves upon each by providing a means for calibrating the assumption of DA with human data.

3. General Applicability of the Method

The method is generally applicable for cumulative/mixtures risk assessments applied to humans when data requirements are met, and for risk assessments applied to other animals for which veterinary pharmaceutical data are available. The method may not be applicable to cumulative/mixtures risk assessments for aquatic and other ecological targets, however, companion methods are currently being developed for those applications.

4. Overall Strengths and Weaknesses of the Method

The greatest strengths of the method are that it 1) relies upon species-specific data; in particular, on human data to evaluate human risk, and 2) is well grounded in pharmacological principles of dose response and cumulative effects, which have been demonstrated in humans. For non-human target species, the method would use data specific to those species.

The weaknesses of the method pertain to the requirements for data on potency and mode of action, which will not be available for all chemicals and all species.

5. Minimum Data Requirements and Types of Data Needed to Apply the Method

When available, data characterizing the dose response for adverse outcomes and modes of action of the chemicals of interest in humans are optimal. In its absence, data are necessary for characterizing the adverse outcomes and/or mode of action of the chemicals of interest in experimental animals, as well as data for human pharmaceuticals or endogenous substances (hormones, neurotransmitters, etc.) that operate by similar modes of action and/or cause the same or physiologically similar adverse outcome in humans. If a non-human species were the receptor of interest, analogous data for veterinary pharmaceuticals and endogenous

substances would be required. In practice, information on the mode of action for chemicals and pharmaceuticals is helpful and necessary for full application of the HRPT method. Data suggesting DA effects for mixtures of the chemicals of interest is not necessary (i.e, it is the default assumption), but is helpful in determining the degree of conservatism imparted by the HRPTs developed from the data.

6. Does this Case Study:

A. Describe the dose-response relationship in the dose range relevant to human exposure?

Yes; this case study presents a compilation of clinical data from human pharmaceuticals and compares the effects of those pharmaceuticals in humans to their effects in laboratory rats.

B. Address human variability and sensitive populations?

Yes; indirectly. The method incorporates an order of magnitude conservatism in the recommendation of HRPT values, which is considered sufficient to protect sensitive subpopulations.

C. Address background exposure or responses?

Yes; the issue of background exposure and responses is considered through the fundamental principles of receptor and enzyme affinity, intrinsic activity, and efficacy.

D. Address incorporation of existing biological understanding of the likely mode of action?

Yes; this issue is fundamental to analysis and rejection of the DA-CAOS concept and its refinement through development of the HRPT approach.

E. Address other extrapolations, if relevant; e.g., insufficient data; duration extrapolations; interspecies extrapolation?

Yes; the HRPT method specifically addresses interspecies extrapolation by using actual human data to evaluate the level at which animal data demonstrating DA effects can be extrapolated to humans. The method could be used as well to address other target species where species-specific data are available.

F. Address uncertainty?

The HRPT method is intended to directly address uncertainties in the DA-CAOS approach and to reduce those uncertainties by using human data to calibrate the assumption of DA for human risk assessments.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?

Yes; the method builds upon common risk assessment methods for chemical mixtures.

H. Work practically? If the method still requires development, how close is it to practical implementation?

Yes; the method is believed to work practically. The HRPT is not a replacement for, but a refinement that can be added to the methods for mixtures risk assessment commonly employed by the US EPA as well the DA-CAOS approach proposed by the NRC. Practical application of the HRPT method has been demonstrated for some groups of chemicals with anti-androgenic potential (Borgert et al. 2012). It could be tested and further refined through application to more example chemicals with varied modes of action.

7. REFERENCES

Benson R. 2009. Hazard to the developing male reproductive system from cumulative exposure to phthalate esters--dibutyl phthalate, diisobutyl phthalate, butylbenzyl phthalate, diethylhexyl phthalate, dipentyl phthalate, and diisononyl phthalate. Regulatory Toxicology and Pharmacology 53(2): 90-101.

Borgert CJ, Sargent EV, Casella G, Dietrich DR, McCarty LS, Golden RJ. (2012). The human relevant potency threshold: reducing uncertainty by human calibration of cumulative risk assessments. Regul Toxicol Pharmacol *62*, 313-328.

Kortenkamp A, Faust M. 2010. Combined exposures to anti---androgenic chemicals: Steps towards cumulative risk assessment. International Journal of Andrology, 33(2): 463-74.

Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Raaij MV, & Vickers C. (2011). Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. *Regulatory Toxicology and Pharmacology 60:* S1-S14.

NRC (National Research Council) (2008). Phthalates and Cumulative Risk Assessment: The Task Ahead. Washington, DC: The National Acadamies Press.

Safe SH. 1990. Polychlorinated biphenyls (pcbs), dibenzo-p-dioxins (pcdds), dibenzofurans (pcdfs), and related compounds: Environmental and mechanistic considerations which support the development of toxic equivalency factors (tefs). Critical Reviews in Toxicology, 21(1): 51-88.