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Interim Guidance

Thyroid Disrupting Pesticides: Use of Rat Thyroid Data and Application of Uncertainty Factors for RfD Derivation

The objective of this paper is to provide guidance on the use of toxicokinetic or dynamic information to replace the current standard default 10X uncertainty factors which are applied to address interspecies and interindividual (human) differences in the dose–response assessment for pesticides that have been shown to disrupt thyroid function in rats. This guidance is considered interim until more experience is gained on the ability of chemicals to disrupt thyroid function during pregnancy as well as in prenatal and postnatal periods of neurodevelopment.

This guidance will largely focus on the interspecies differences between rat and human thyroid function. It is anticipated that the standard intraspecies factor of 10X (used to account for human variability in toxicokinetics and toxicodynamics) will likely be retained unless sufficient human thyroid data and quantitative analyses are available to replace it. However, as discussed below, the standard default interspecies factor of 10X (used to account for animal to human differences in toxicokinetics and toxicodynamics) may be reduced with respect to observed thyroid effects in the rat depending on the data situation. It should be noted that the traditional interspecies (as well as the intraspecies) 10X uncertainty factor is subdivided into a factor of 3X (3.16) for toxicokinetics¹ and a 3X (3.16) for toxicodynamics².

In selecting endpoints for establishing points of departure, the most reliable and sensitive endpoint associated with thyroid perturbation should be considered such as hormone measures, enhanced glucuronyl transferase (UDPGT) activity, increases in liver or thyroid weights, thyroid hypertrophy or pathology. In dealing with the interspecies and database uncertainty factors, three common scenarios are described below and depicted in Table 1.

¹ *Toxicokinetics*: the process of the uptake of potentially toxic substances by the body, the biotransformation they undergo, the distribution of the substances and their metabolites in the tissues, and their elimination from the body. Both the amounts and the concentrations of the substances and their metabolites are studied.

² *Toxicodynamics*: the process of interaction of chemical substances with target sites and the subsequent reactions leading to adverse effects.

Situation 1: When there are no prenatal or postnatal thyroid rat data and the point of departure (e.g., a no-observed-adverse-effect level-NOAEL or benchmark dose-BMD) for thyroid effects is based on data from adult rats, a 10X database uncertainty factor should be applied to address potential prenatal and postnatal toxicity and to account for these missing data. (This database uncertainty factor addresses the FQPA concern for the young). The extrapolation of risk will be based on adult rat data to the representative average adult human. Because of toxicodynamic differences in adult thyroid function that result in greater sensitivity of the adult rat to hypothyroidism compared to adult humans (see rationale below), the 3X toxicodynamic part of the 10X interspecies factor can be removed leaving the 3X portion for toxicokinetic interspecies differences. Thus, the usual 100X uncertainty factor for intra- and interspecies differences is reduced to 30X. A 10X factor for database uncertainty is applied, thus resulting in a total composite uncertainty factor of 300X. The toxicokinetic 3X portion of the interspecies factor should be retained, unless sufficient pharmacokinetic data and quantitative analyses, such as models, are available to replace it.

Situation 2: When there are acceptable prenatal and postnatal thyroid data available³, then the 10X data database uncertainty factor can be removed. If these thyroid data establish that the young animal **is more sensitive**, then the standard interspecies factor should be retained at 10X because the young is the target population and the basis of the point of departure (POD) for deriving the RfD (i.e., equivalent animal POD for the fetal or postnatal rat is extrapolated to equivalent or representative human fetus or young child). In this situation, the 3X portion of the standard 10X interspecies factor for toxicodynamic differences can not be removed because currently differences in the toxicodynamics for the developing thyroid function between rats and humans are not well understood. Thus, the standard 10-fold factors for intra- and interspecies differences collapses back to the usual 100-fold factor in the absence of appropriate toxicokinetic and toxicodynamic data.

³ Recent guidance (October 24, 2005 **Guidance for Thyroid Assays in Pregnant Animals, Fetuses and Postnatal Animals, and Adult Animals**, Office of Pesticide Programs, Health Effects Division, Washington DC) has been developed on the type of data to generate for purposes of establishing NOAELs and LOAELs (or benchmark doses) that may be used to derive RfDs that would be protective of the ability of a chemical to disrupt thyroid function in pregnant females and in the fetus and newborn.

Situation 3: When there are acceptable prenatal and postnatal thyroid data available (see footnote 3), then the 10X data database uncertainty factor can be removed. If these thyroid data establish that the young are **not more sensitive** compared to the adult, then the interspecies factor should be reduced to 3X because extrapolation of risk will be based on adult rat data to the representative human (*i.e.*, the adult). As discussed above in situation 1, the interspecies factor is reduced to 3X to account for the increase sensitivity of the adult rat to hypothyroidism compared to adult humans (see rationale below). Thus, the usual 100X uncertainty factor for intra- and interspecies differences is reduced to 30X. The 10X factor for database uncertainty is also removed resulting in a total composite uncertainty factor of 30X. The toxicokinetic 3X portion of the interspecies factor should be retained, unless sufficient pharmacokinetic data and quantitative analyses, such as models, are available to replace it.

Rationale for the reduction of the interspecies factor for adult animal (*i.e.*, rat) to human extrapolations:

The 3X portion of the 10 X for interspecies toxicodynamic differences can be removed because of several important quantitative dynamic differences between rats and humans with respect to thyroid function. The half-life of T4 in rats is approximately 12 hours, whereas in humans, the half-life is 5-9 days (Dohler *et al.*, 1979). The shorter half-life is likely related to a high-affinity binding globulin for thyroxin that is present in humans, but absent in adult rodents. Binding of the hormone to thyroid binding globulin accounts for slower metabolic degradation and clearance. Increased turnover and hepatic clearance of T3 and T4 renders the basal activity of the rat thyroid gland markedly more active than in humans. In the absence of a functional thyroid gland, a rat requires approximately 10-times more T4 than an adult human for full reconstitution (Dohler *et al.*, 1979). Constitutive TSH levels are nearly 25-times higher in rats than in humans, reflecting the increased activity of the thyroid-pituitary axis in rats (Dohler *et al.*, 1979; McClain, 1992).

References

- Dohler, K. D., Wong, C. C., Von Zur Muhlen, A. (1979) The rat as a model for the study of drug effects on thyroid function: Consideration of methodological problems. *Pharmacol. Ther.* 5, 305-318
- McClain, R. M. (1992). Thyroid gland neoplasia: non-genotoxic mechanisms. *Toxicol. Lett.* 64/65, 397-408.

TABLE 1. Thyroid Data Situations and Application of Standard Uncertainty Factors

Rat Thyroid Data	Interspecies UF	Intraspecies UF	FQPA SF*	Total
Adult only	3X	10X	10X	300X
Adult & pups <u>(pups more sensitive and NOAEL is based on postnatal data)</u>	10X	10X	--	100X
Adult & pups <u>(pups not more sensitive and NOAEL is based on adult data)</u>	3X	10X	—	30X

* Guidance has been developed on generating data to evaluate thyroid toxicity in young animals. See footnote 3.