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MEMORANDUM

SUBJECT: **Propanil**. Addendum to the Revised Human Health Risk Assessment

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This memorandum summarizes revisions to the propanil human health risk assessment following the submission of a new toxicology study and a re-evaluation by the HED Hazard Identification Assessment Review Committee (HIARC). Risk assessment revisions have been made for chronic dietary risk and for drinking water levels of comparison (DWLOCs). Occupational risk estimates have not been revised and remain as provided in the 2/28/02 risk assessment.

On January 8, 2003 the Propanil Task Force submitted a non-guideline 30-day, repeated dose, oral (dietary) toxicity study in rats (MRID 45829301) as requested by the Agency. This dietary study in the rat assessed methemoglobin levels at serial time points. Following review by HED, the HIARC convened on March 27, 2003 to determine use of the study in selecting appropriate endpoints and doses for human health risk assessment. In addition to consideration of this study, the HIARC

reevaluated the data base in accordance with the February 28, 2002 OPP guidance document, "*Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment*."

At the March 27, 2003 meeting, the HIARC determined the following: 1) No special FQPA safety factor is needed (i.e., 1X) since there are no residual uncertainties for pre- and postnatal toxicity. 2) The weight of the evidence in the propanil data base supports a receptor-mediated endocrine mode of action (MOA), rather than a neurologically-mediated endocrine MOA; on that basis, it was concluded that a developmental neurotoxicity study is not required. 3) An *in vitro* androgen receptor binding assay is required to provide confirmation of the putative endocrine mode of action for propanil; the need for additional *in vivo* testing will be determined based upon the results of the *in vitro* assay. 4) For dietary and residential risk assessments, a 3X data base uncertainty factor (UF_{DB}) is sufficient to account for the uncertainties associated with the absence of the receptor binding assay and/or any additional *in vivo* testing that may be required, and for all risk assessments that utilize the methemoglobin endpoint from the chronic rat study, a 3X LOAEL-to-NOAEL uncertainty factor (UF_L) is sufficient to account for the lack of a NOAEL. 5) No appropriate effects attributed to a single exposure (dose) were identified in any study including the rat or rabbit developmental toxicity studies, or the special non-guideline single- and repeated-dose methemoglobin study.

Chronic Population Adjusted Dose (cPAD): The HIARC concluded that methemoglobin levels in the non-guideline methemoglobin study were adversely affected in male and female rats following 5 or more repeated doses of propanil at doses of 25 and 28 mg/kg/day (the lowest dose tested in males and females). Therefore, the special methemoglobin study did not provide doses that could be used in repeated-dose dietary/oral risk assessments for propanil (since the LOAEL from the chronic study was previously established at 9 mg/kg/day).

Dose and Endpoint for Establishing RfD: As in the revised risk assessment of 2/28/02, the dose level selected for chronic dietary risk assessmentr is 9 mg/kg/day (LOAEL) based on increased methemoglobin and increased spleen weight in females, and observations of small seminal vesicles and prostates in males.

Uncertainty Factor(s): The combined uncertainty factor for the propanil cPAD has been revised from 3,000 (as in the 2/28/02 assessment) to 1,000 (10X for interspecies extrapolation, 10X for intraspecies variability, and 10X for LOAEL-to-NOAEL [3X UF_L] plus database uncertainty [3X UF_{DB}]).

The HIARC determined that a 3-fold factor would be sufficient to address the NOAEL to LOAEL uncertainty, based upon the following rationale: It was noted that in the chronic/carcinogenicity study in rats the increases in methemoglobin at the low

dose of 9 mg/kg/day were not significant for males at any time point evaluated. For low-dose females (11.5 mg/kg/day) the increases were significant at weeks 13, 26, and 52, but not at 78 or 104/105. These data demonstrate a NOAEL for increased methemoglobin at 9 mg/kg/day in males and suggest that the low-dose findings in females are very likely near the threshold of response. This indicates that a 3-fold uncertainty factor should be adequate for the extrapolation of LOAEL to NOAEL for this endpoint.

A database uncertainty factor of 3X is applied for the absence of an assessment of anti-androgenic potential (i.e., an *in vitro* androgen receptor binding assay and/or an *in vivo* special developmental toxicity study to evaluate the effect of propanil on male reproductive system development). The HIARC considered a 3-fold UF_{DB} to be sufficient to address these uncertainties, based upon the following rationale. 1) Evidence of possible endocrine-related toxicity (delayed sexual maturation in both sexes, and decreased sperm count and production rate in males) was observed only in the two-generation reproduction study at doses of 53 and 61 mg/kg/day in F1 males and females, respectively, and 2) increased methemoglobin measures were observed in the chronic/oncogenicity study in rats at a dose level of 9 mg/kg/day. The methemoglobin findings, an extremely sensitive toxic response to propanil exposure, were utilized universally for endpoint and dose selection in the risk assessments for propanil, that is, at approximately 6 times below the dose where possible endocrine-related effects were observed; thus, a 3-fold UF_{DB} factor should be adequate.

$$\textbf{Chronic PAD} = \frac{9.0 \text{ (LOAEL) mg/kg/day}}{1{,}000 \text{ (UF)}} = \textbf{0.009 mg/kg/day}$$

Revised Dietary Risk and DWLOC Estimates: Chronic dietary risk estimates have been revised to reflect the revision of the cPAD from 0.003 mg/kg bw/day to 0.009 mg/kg bw/day. The revised risk estimates also reflect an update to the food consumption database that is the basis for dietary risk assessment.

Consumption / Model Data: The propanil chronic dietary exposure assessment (S. Kinard memo, 5/20/03) was conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.3) which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994 -1996 and 1998. The 1994 - 96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Risk is reported for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old. Exposure estimates are reported in mg/kg body weight/day, and risk is expressed as a percent of the cPAD.

Revised Dietary Risk Estimates

Population	Exposure mg/kg/day	% Chronic PAD
U.S. Population	0.000175	2
All Infants (<1 year)	0.000314	4
Children 1-2 years	0.000394	4
Children 3-5 years	0.000347	4
Children 6-12 years	0.000236	3
Youth 13-19 years	0.000165	2
Adults 20-49 years	0.000161	2
Females 13-49	0.000134	2
Adults 50+ years	0.000112	1

Chronic Drinking Water Levels of Comparison: The chronic DWLOC estimates for propanil have also been revised based on the revised dietary risk estimates. The following equation was used to calculate the chronic DWLOC value required for propanil aggregate risk assessment:

$$DWLOC_{chronic}\ (\mu g/L) = \frac{[\text{allowable chronic water exposure (mg/kg/day) x (kg body weight)}]}{[\text{consumption (L/day) x } 10^{-3}\ \text{mg/}\mu g]}$$

where, allowable chronic water exposure (mg/kg/day) = cPAD (0.009 mg/kg/day) minus estimated chronic food exposure (mg/kg/day). DWLOCs are calculated for males, females, and children based on default water consumption estimates of two liters per day for male and female adults, and one liter per day for children.

Chronic DWLOC Calculations						
Population Subgroup	**cPAD (mg/kg/day)**	**Chronic Food Exposure (mg/kg/day)**	**Maximum Chronic Water Exposure (mg/kg/day)**	**Groundwater EEC (Rice) (µg/L)**	**Surface Water EEC (Rice) (µg/L) based on propanil *and* 3,4-DCA**	**DWLOC chronic (µg/L)**
Children	0.009	0.000394	0.008606	0.4	Range of: 6 - 72	86
Females	0.009	0.000134	0.008866	0.4	6 - 72	266
Males	0.009	0.000196	0.008804	0.4	6 - 72	308

The EEC estimates for propanil *per se* and 3,4-DCA (combined) are less than the estimated DWLOC; and a conclusion can be drawn (based on the cPAD approach) that no adverse toxicological effect will occur due to aggregate chronic exposure.