

4. *Cumulative exposure to substances with a common mechanism of toxicity.* Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether mesotrione has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, mesotrione does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that mesotrione has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the final rule for Bifenthrin Pesticide Tolerances (62 FR 62961, November 26, 1997).

D. Safety Factor for Infants and Children

1. *In general.* Section 408 of the FFDCA provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the data base on toxicity and exposure unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessments either directly through use of a MOE analysis or through using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk to humans.

2. *Prenatal and postnatal sensitivity.* There is quantitative evidence of increased susceptibility demonstrated in the oral prenatal developmental toxicity studies in rats, mice, and rabbits.

Delayed ossification was seen in the fetuses at doses below those at which maternal toxic effects were noted. Maternal toxic effects in the rat were decreased body weight gain during treatment and decreased food consumption and in the rabbit, abortions and GI effects.

3. *Conclusion.* There is a complete toxicity data base for mesotrione and exposure data are complete or are estimated based on data that reasonably accounts for potential exposures. The FQPA safety factor (10x) is retained in assessing the risk posed because there is quantitative evidence of increased susceptibility of the young exposed to mesotrione in the prenatal developmental toxicity studies in mice, rats, and rabbits and in the multi-generation reproduction study in mice, there is qualitative evidence of increased susceptibility of the young exposed to mesotrione in the multi-generation reproduction study in rats; and a Developmental Neurotoxicity Study is required to assess the effects of tyrosinemia on the developing nervous system exposed to mesotrione.

E. Aggregate Risks and Determination of Safety

To estimate total aggregate exposure to a pesticide from food, drinking water, and residential uses, the Agency calculates DWLOCs which are used as a point of comparison against the model estimates of a pesticide's concentration in water (EECs). DWLOC values are not regulatory standards for drinking water. DWLOCs are theoretical upper limits on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food and residential uses. In calculating a DWLOC, the Agency determines how much of the acceptable exposure (i.e., the PAD) is available for exposure through drinking water [e.g., allowable chronic water exposure (mg/kg/day) = cPAD - (average food + residential exposure)]. This allowable exposure through drinking water is used to calculate a DWLOC.

A DWLOC will vary depending on the toxic endpoint, drinking water consumption, and body weights. Default body weights and consumption values as used by EPA are used to calculate DWLOCs: 2 liter (L)/70 kg (adult male),

2L/60 kg (adult female), and 1L/10 kg (child). Default body weights and drinking water consumption values vary on an individual basis. This variation will be taken into account in more refined screening-level and quantitative drinking water exposure assessments. Different populations will have different DWLOCs. Generally, a DWLOC is calculated for each type of risk assessment used: Acute, short-term, intermediate-term, chronic, and cancer.

When EECs for surface water and ground water are less than the calculated DWLOCs, OPP concludes with reasonable certainty that exposures to the pesticide in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of aggregate human health risk at this time. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of comparison in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of residues of the pesticide in drinking water as a part of the aggregate risk assessment process.

1. *Acute risk.* Acute doses and endpoints were not selected for the general U.S. population (including infants and children) or the females 13-50 years old population subgroup for mesotrione; therefore, acute dietary risk is not expected.

2. *Chronic risk.* Using the exposure assumptions described in this unit for chronic exposure, EPA has concluded that exposure to mesotrione from food will utilize 2.1% of the cPAD for the U.S. population, 4.4% of the cPAD for infants (<1 year old) and 5.0% of the cPAD for children 1-6 years old. There are no residential uses for mesotrione that result in chronic residential exposure to mesotrione. In addition, there is potential for chronic dietary exposure to mesotrione in drinking water. After calculating DWLOCs and comparing them to the EECs for surface and ground water, EPA does not expect the aggregate exposure to exceed 100% of the cPAD, as shown in the following Table:

AGGREGATE RISK ASSESSMENT FOR CHRONIC (NON-CANCER) EXPOSURE TO MESOTRIONE

Population Subgroup	cPAD mg/kg/day	% cPAD (Food)	Surface Water EEC (ppb)	Ground Water EEC (ppb)	Chronic DWLOC (ppb)
U.S. Population	0.0 007	2.1	4.3	0.1 5	24
Infants (<1 year old)	0.0 007	4.4	4.3	0.15	6.7
Children (1-6 years old)	0.0 007	5.0	4.3	0.15	6.7