

as an endocrine-disrupting substance. EPA stresses that no evidence of estrogenic or other endocrine effects have been noted in any of the toxicology studies that have been conducted with this product and there is no reason to suspect that any such effects would be likely. Due to the millions of Americans and their children exposed to glufosinate and its metabolites, EPA needs to conclusively determine if this herbicide has endocrine-disrupting potential.

Agency response. EPA is required under the FFDCA, as amended by the FQPA, to develop a screening program to determine whether certain substances, including all pesticide active and other ingredients, "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, glufosinate ammonium may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption. The studies submitted as guideline studies as well as the data reviewed in the open literature did not provide any obvious indications that glufosinate ammonium and/or its metabolites have specific endocrine disruptive effects.

8. Comment—dietary exposure. EPA states that tolerances have been established (40 CFR 180.473) for the combined residues of glufosinate ammonium and metabolites in or on a variety of RACs. EPA further maintains that no appropriate toxicological endpoint attributable to a single exposure was identified in the available toxicity studies. This is why EPA has

not established an acute RfD for the general population including infants and children. An acute RfD of 0.063 mg/kg/day was established, however, for the females 13+ subgroup. Therefore, an acute dietary analysis was conducted for this sub-population; whereas, chronic dietary analysis was conducted for the usual populations. We request that EPA reconsider and reevaluate the health information finding that no appropriate toxicological endpoint attributable to a single exposure was identified in the available toxicity studies as too being limited and erroneous.

Agency response. EPA has evaluated the published toxicity studies and considered the relevant petitioner submitted studies. On the basis of these studies, no appropriate endpoint of concern attributable to a single exposure was identified. EPA has asked the petitioner to conduct a study to evaluate potential effects of glufosinate ammonium following a single exposure (acute effects) with glutamate synthetase measurements. Until such data are available, EPA has applied additional data base UF to account or allow for uncertainty about those potential effects of acute exposure.

9. Comment—infants and children. We are very concerned that EPA finds that the toxicological data base is sufficient for evaluating prenatal and postnatal toxicity for glufosinate ammonium in human infants and children using exclusively results from rats and rabbits. Although EPA states that there are no prenatal or postnatal susceptibility concerns for infants and children, based on the results of the rat and rabbit developmental toxicity studies and the 2-generation reproduction study, we are concerned that human infants and children may possess genetic predispositions, biochemical individualities and behavioral patterns very different from rats and rabbits. EPA needs to do a more thorough literature review and interview scientists and medical doctors who may have relevant information on the prenatal and postnatal toxicity for glufosinate ammonium in human infants and children.

As EPA notes, Based on clinical signs of neurological toxicity in short and intermediate dermal toxicity studies with rats, the agency has determined that an added FQPA safety factor of 3x is appropriate for assessing the risk of glufosinate ammonium derived residues in crop commodities. Using the conservative assumptions described in the exposure section above, the percent of the chronic RfD that will be used for exposure to residues of glufosinate ammonium in food for children 1–6 (the

most highly exposed sub-group) is 61%. Infants utilize 37% of the chronic RfD. As in the adult situation, drinking water levels of comparison are higher than the worst case DWECs and are expected to use well below 100% of the RfD, if they occur at all. Therefore, there is a reasonable certainty that no harm will occur to infants and children from aggregate exposure to residues of glufosinate ammonium.

Agency response. The short-term (dermal, inhalation, and incidental oral) and acute dietary (females 13–50 years) endpoints are based on reduced fetal body weight and increased fetal death seen in the rabbit developmental toxicity study (6.3 mg/kg/day). An acute dietary endpoint for the general population, including infants and children, could not be identified due to no adverse effects seen in the relevant studies. The chronic dietary endpoint is based on a weight-of-evidence approach from several studies which demonstrated brain glutamine synthetase inhibition and alterations in the electrocardiogram (6.0 mg/kg/day). EPA concluded that the toxicological data base for glufosinate ammonium was not complete and requested the submission of the following studies: (1) Acute neurotoxicity study conducted in the rat which includes glutamine synthetase activity measurement in the liver, kidneys, and brain; (2) a developmental neurotoxicity (DNT) study conducted in the rat which includes comparative glutamine synthetase activity measurement in the liver, kidneys, and brain of the pups and mothers; and (3) a 28-day inhalation toxicity study in rats with glutamine synthetase activity measurements in brain, kidney, liver and lung. EPA also requested additional data to confirm that liver and kidney changes, observed in the absence of histopathological changes, are an adaptive response and not an adverse effect. Kidney and liver function assays should be performed in addition to glutamine synthetase activity measurements. Pending the submission of the requested data, a 10x data base uncertainty factor was applied to all oral and dermal risk assessments and a 100x uncertainty factor was applied to all inhalation risk assessments. These uncertainty factors combined with the traditional 100x inter/intra species uncertainty factor, resulted in a total uncertainty factor of 1,000x for dermal and oral exposure assessments and 3,000x for inhalation exposure assessments (10,000x uncertainty factor reduced to 3,000x based on Agency policy cited in Unit III.B.).