

0.05 ppm. For further information on EPA's rationale for assuming half LOQ residues see "Values to Non-Detectable/Non-Quantifiable Residues in Human Health Food Exposure Assessments" (faxed upon request; telephone: (202) 401-0527; item: 6047).

3. *Comment—magnitude of glufosinate residues.* The reason that we are requesting independent sampling and gas chromatography analyses be conducted besides that performed by Aventis and its contractors is the potential for higher glufosinate residue concentrations to be confirmed above the 0.74 ppm level in rice grain and 1.48 ppm level in rice straw when sampled at 70 days or more after the last treatment. We are concerned that Aventis' sampling protocol may have been biased in some unidentified manner and that samples above the 0.74 ppm level in rice grain and 1.48 ppm level in rice straw were missed in the field residue trials. While EPA emphasizes that the treatment regime was selected to represent the use pattern that is the most likely to result in the highest residues, we are concerned that sampling bias may have transpired and resulted in bias in the G.C. analyses. We are also concerned that glufosinate treatment may have occurred closer to the sampling period than is the case and higher glufosinate concentrations were missed. After all, a higher concentration factor of approximately 2.3 was found for rice hulls compared to the grain and straw. We also question that the finding that no detectable concentration of the residues occurred when rice whole grain was processed into polished grain and bran, whereas a glufosinate residue concentration may have been present at less than the 0.05 ppm (50 ppb) detection limit.

Agency response. The rice magnitude of the residue (15 field trials conducted throughout the rice growing regions in the United States; 2 composite samples collected at each site) and processing studies were conducted according to the regulatory guideline requirements (OPPTS 860.1500 and 860.1520) and conformed to EPA GLP Standards. It is difficult to further address the potential for bias since the comment gave no specific criteria for the concern. The comment does make reference to the processing study and the concentration of residues in rice hull and the lack of concentration of residues in rice bran and polished rice. The following paragraph is a summary of the rice processing study.

Processing studies are required to determine if residues reduce or concentrate during food processing (processing factor = concentration in

processed commodity ÷ concentration in unprocessed commodity). Processing factors are dependent on several factors including the location of the residues (surface or translocated residues), loss of water as in dried commodities, and/or the physical chemical properties of the residues. The rice processing study (conducted at 5x the proposed rate) resulted in quantifiable concentrations of glufosinate ammonium, *N*-acetyl-glufosinate, and 3-MP in/on all commodities excluding glufosinate ammonium and *N*-acetyl-glufosinate in/on rice hull (residues at the LOQ assumed for calculation of processing factor). Based on the combined glufosinate ammonium, *N*-acetyl-glufosinate, and 3-MP residues in/on the processed and unprocessed commodities, the following processing factors were calculated: rice hull—2.8x, rice bran—0.9x, and polished rice—1.3x. The dietary analyses assumed average field trial residues and a processing factor of 1.3 for all rice commodities excluding rice bran where a processing factor of 0.9 was assumed (rice hull is not a human food commodity).

4. *Comment—acute toxicity.* EPA states that glufosinate ammonium has been classified as toxicity category III for acute oral, dermal, and inhalation toxicity; and for eye irritation. EPA finds that glufosinate ammonium is not a dermal irritant (toxicity category IV) nor is it a dermal sensitizer. The oral LD₅₀ is 2 g/kg in male rats, and 1.62 g/kg in female rats. But we are concerned about acute toxicity because of the published finding that glufosinate causes convulsions in humans and experimental rodents by brain cell glutamate receptor activation (glufosinate and glutamate are structurally similar) according to Matsumura et al. Has EPA considered the structural similarities between glufosinate and glutamate receptor activation. We request that EPA review all of the relevant toxicological literature on human and rat brain cell glutamate receptor activation and speak with scientists who performed this research as to the significance of glufosinate tampering with glutamate receptors. Evidence also exists that glufosinate stimulates nitric oxide production in the brain through *N*-methyl-D-aspartate (NMDA) receptors. We request that EPA investigate this published finding to determine if the requested herbicide tolerance concentrations are set too high which, is a possibility.

Agency response. EPA has evaluated both the published and petitioner submitted toxicity studies. The oral,

dermal, and inhalation toxicity categories assigned by EPA are based on studies conducted according to the EPA toxicity testing guidelines and were conducted in compliance with EPA GLP. In an acute oral toxicity study in rats, the oral LD₅₀ was found to be 1,620 and 2,000 mg/kg/day in female and male rats, respectively. In this study, no effects were seen in rats at doses up to 630 mg/kg/day.

The commenter cites two acute exposure studies. Matsumura et al. have shown that an acute dose of 80 mg/kg injected intraperitoneally into mice was convulsive and that this effect was partially antagonized by NMDA antagonists, suggesting that NMDA receptors may mediate this effect. Nakaki et al. found that injection of glufosinate ammonium directly into the brain stimulated nitric oxide production as a result of stimulation of NMDA receptors in rat brain, another neurochemical effect. But neither of these published studies provide sufficient appropriate evidence to establish an acute endpoint for risk assessment from oral, dermal, or inhalation exposures because the routes that they used, intraperitoneal injection or direct injection into the brain, are not directly relevant to potential routes of human exposure to pesticides, i.e., oral, dermal, or inhalation exposure.

The herbicidal mechanism of action of glufosinate ammonium is inhibition of the enzyme glutamine synthetase. This enzyme is also present in mammalian systems. In mammals, glutamine synthetase facilitates the conversion of glutamate and ammonia to glutamine and is therefore involved in the metabolism of nitrogen and ammonia. In addition, glutamate is a major excitatory neurotransmitter in the nervous system; inhibition of glutamine synthetase has been shown to impair its ability to serve as a neuroprotectant by controlling glutamate concentrations in neurons. More generally in the body, ammonia is buffered for extracellular transport through its interaction with glutamate to form glutamine by glutamine synthetase.

EPA also reviewed mechanistic studies submitted by the petitioner as well as the published studies, and, where applicable and appropriate, incorporated findings from these studies in the human health risk assessment. In fact, the intermediate-term and long-term incidental oral endpoints and the chronic dietary endpoint are based on brain glutamine synthetase inhibition, the most sensitive indicator of glufosinate ammonium toxicity in humans and experimental animals.