

After reviewing all of the submitted data, EPA confirms that the tolerances, as proposed, are safe.

5. *Comment—genotoxicity.* EPA claims that ... based on results of a complete genotoxicity data base, there is no evidence of mutagenic activity in a battery of studies, including: *Salmonella* spp., *E. coli*, *in vitro* mammalian cell gene mutation assays, mammalian cell chromosome aberration assays, *in vivo* mouse bone marrow micronucleus assays, and unscheduled DNA synthesis assays. EPA needs to inquire with the FDA, USDA, ATSDR, medical doctors and scientists as to whether there are reports of glufosinate induced mutations and gene toxicity which appear to be glossed over in the Aventis petition.

*Agency response.* Glufosinate ammonium was clearly negative in the acceptable guideline mutagenicity studies. The test battery included: a *Salmonella typhimurium* and *Escherichia coli* reverse gene mutation assay, *in vitro* mammalian cell gene mutation and chromosome aberration assays, *in vivo* mouse bone marrow micronucleus assay and an *in vitro* unscheduled DNA synthesis assay. All studies were performed in accordance with the specified Office of Prevention, Pesticides, and Toxic Substances (OPPTS) Harmonized Mutagenicity Test Guidelines Series 870 and satisfied the testing requirements of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Toxic Substances Control Act (TSCA), and the Organization for Economic Cooperation and Development (OECD). Further, each study meets the requirement of 40 CFR part 160, Good Laboratory Practice (GLP) and was subjected to a Quality Assurance (QA) inspection. Based on the negative responses observed in these assays, EPA concluded that there is no concern for mutagenicity from exposure to glufosinate ammonium. In addition, no evidence of carcinogenicity was observed in mice and rats in acceptable guideline carcinogenicity studies. As indicated previously, EPA evaluated both petitioner submitted guideline studies and published scientific studies. In addition, the petitioner is required by law under FIFRA (6)(a)(2) to report any adverse finding to EPA.

No mutagenicity studies were found in the open literature and the Agency for Toxic Substances and Disease Registry (ATSDR) has no finalized, draft, or "under development" toxicological profile for glufosinate ammonium. Finally, FDA has evaluated the human safety of multiple crops with resistance to glufosinate ammonium and has no concerns for human safety but has no mutagenicity or toxicity data in

the Biotechnology Notification Files on this herbicide.

6. *Comment—reproductive and developmental toxicity.* We are skeptical of EPA's findings because, based on peer-reviewed studies in the published literature, birth defects have been caused by exposure of the human father to the herbicide. EPA needs to thoroughly investigate these findings and reconsider the glufosinate herbicide tolerance limits requested by Aventis as entirely unsafe and unacceptably high. It is rather distressing to note that there does not seem to be peer reviewed studies on the metabolism of the high levels of acetyl glufosinate in harvested GM crops to highly neurotoxic and teratogenic glufosinate. Certainly, gut bacteria are well known to contain enzymes that remove acetyl groups from glufosinate and mammalian enzymes may also be capable of removing the acetyl group from glufosinate. Even though glufosinate is being used widely with GM crops in North America its safety is far from proven and its impact on humans and farm animals is difficult to trace because the GM products are not labeled for consumption. We request that EPA obtain more technical data and information to better define the neurotoxicity and teratogenicity of glufosinate and its metabolites, especially in humans. Glufosinate, for example, was found to trigger apoptosis (programmed cell suicide) in the developing brain of the embryonic mouse. Numerous, well established studies showing brain damage and birth defects seem to have been ignored by those regulating use of the herbicide. We request that the EPA conduct a more comprehensive investigation of available literature on glufosinate and make requests for unpublished information from independent scientists such as their expert opinions on the adverse health effects of glufosinate and its metabolites.

We request the same under subchronic, chronic, animal metabolism, and metabolite toxicology as requested for Reproductive and Developmental toxicity.

*Agency response.* The study authors (cited study by Garcia et al) state in their conclusion that "these findings warrant further investigation." In this study, only 16 individuals out of 261 referenced glufosinate ammonium. The results of this study indicated that there was a marginally significant increased risk of paternally related developmental toxicity. However, in this study various contributing factors such as smoking, work habits etc. were not evaluated and therefore, this epidemiological evaluation does not establish a causal

definitive link to paternally related developmental toxicity. The potential for glufosinate ammonium to cause developmental or reproductive effects due to exposure (male or female) has been evaluated in acceptable guideline studies in rats and rabbits. Based on these studies, glufosinate ammonium is not teratogenic in rats and rabbits.

The petitioner has submitted acute, subchronic, chronic, developmental, and reproductive toxicity studies conducted with glufosinate ammonium. The petitioner has also submitted developmental toxicity studies (rat and rabbit) and subchronic studies (rat, mouse, and dog) with *N*-acetyl-glufosinate and 3-MP. All of these studies were conducted according to the regulatory guideline requirements (OPPTS 870 series) and conformed to EPA GLP Standards. EPA has reviewed all of these studies and selected the most sensitive endpoints. Based on a comparison of the common studies conducted with the parent and metabolites, the metabolites exhibited toxic effects at doses equal to or greater than the parent and EPA concluded that *N*-acetyl-glufosinate and 3-MP are not likely to be more toxic than glufosinate ammonium. In regards to the enzyme that can remove acetyl groups from substrates, these enzymes are present in the toxicology test systems used to evaluate the parent and metabolites.

In the cited study by Watanabe, mouse embryo cultures were exposed to glufosinate ammonium. This is an *in vitro* experiments which indicate apoptosis in the developing brain of cultured mouse embryos. It should be noted that apoptosis is a normal part of the brain development process. This experiments did not use whole animals and the current scientific knowledge is not sufficient to allow extrapolation of *in vitro* results to whole animals.

7. *Comment—endocrine disruption.* We find EPA's statements on the potential of glufosinate to function as an endocrine-disrupting substance in humans and animals as not founded on logical information or peer-reviewed studies. In fact EPA states that no special studies have been conducted to investigate the potential of glufosinate ammonium to induce estrogenic or other endocrine effects. Given the enormous complexities of mammalian hormonal regulatory systems and the current uncertainties existing in this field of knowledge as revealed by EPA's Endocrine Disruptor Advisory Committee several years ago about how to screen for potential endocrine-disrupting substances, we feel it's totally premature for EPA at this time to dismiss all concerns about glufosinate