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MEMORANDUM

DATE: December 3, 2009

SUBJECT: Response to Public Comments on the Preliminary Problem Formulation for the Ecological Risk and Drinking Water Exposure Assessments for Glyphosate and Its Salts

FROM: Pamela Hurley, Ph.D, Senior Toxicologist *Pamela Hurley*
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THRU: Dana Spatz, Branch Chief *Dana Spatz* 12/8/09
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TO: Jude Andreasen, RM 51
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The following paragraphs provide the Environmental Fate and Effects Division (EFED) response to comments on the preliminary problem formulation for the ecological risk, environmental fate, endangered species and drinking water assessments to be conducted as part of the Registration Review of the organophosphate herbicide, glyphosate and its salts.

Monsanto

Comment: Monsanto has requested that the Agency review the entire Problem Formulation document and cited references to “ensure that all rates and concentrations are consistently expressed in terms of acid equivalents (a.e.)...This standardization procedure of expressing rates in terms of glyphosate acid equivalents must also be applied to the ecological endpoints in the ECOTOX database.” In addition, Monsanto notes that there are inconsistencies in whether or not the toxicity endpoints have been corrected for test substance purity.

Response: For the environmental fate and effects section of the glyphosate Registration Review, the Agency will ensure that all rates, toxicity endpoints and concentrations are properly defined and consistently expressed in terms of acid equivalents (a.e.). For the open literature references reported in the ECOTOX database, any papers that may have possible ecological endpoints but do not contain sufficient information to provide a concentration or dose in terms of acid equivalents are normally not considered of sufficient quality to be used for a quantitative assessment of risk.

Comment: Monsanto believes that "a more appropriate chemical description of the class of chemistry to which glyphosate belongs is **phosphono amino acid herbicide**. The use of this term when describing glyphosate would be better understood amongst the chemistry, pesticide-user and regulatory communities."

Response: The Agency acknowledges the comment and will consider using this description when referring to the chemical class to which glyphosate belongs.

Comment: Monsanto provided some suggested changes/deletions to the description of the formulated products (e.g., water-dispersible granules, emulsifiable concentrates, water-dispersible liquids, ready-to-use, soluble concentrate/solid, soluble liquids and water soluble granules).

Agency Response: The Agency will re-examine the labels and if reflected in the labels, the suggested changes will be made to the pesticide usage section.

Comment: Monsanto provided a corrected version of 0.91 for the acid equivalence ratio for the monoammonium counter cation of glyphosate.

Agency Response: The Agency thanks Monsanto for the corrected version, will double check the Agency's assumptions and calculations and if needed, will use the corrected version in future Registration Review documents.

Agency Comment: Monsanto notes that there may be some errors in the toxicity summary tables, including endpoint values, species tested, correcting concentrations to a.i., etc.

Agency Response: The Agency will check these tables for errors/inconsistencies and will provide explanations for any discrepancies between the tables and the Data Evaluation Records (DERs), 1-liner database and the mammalian study values that were generated by the Health Effects Division (HED).

Comment: Monsanto reminds the Agency that in considering the sublethal effects observed in studies from the open literature, the Agency needs to follow the stipulations in the Data Quality Act. Monsanto also requests that the Agency consider the relevance of exposure regimes used during testing.

Response: The Agency agrees that the stipulations in the Data Quality Act need to be followed when the studies from the open literature are considered for use in an assessment of risk. The Agency also notes that sublethal effects are seldom used in a quantitative estimation of risk because reported sublethal effects commonly cannot be quantitatively linked to the toxicity endpoints utilized by the Agency to assess ecological risk (e.g., mortality, growth and reproduction). Therefore, sublethal effects are usually qualitatively characterized in the risk description. The Agency also acknowledges that the relevance of the exposure regime utilized in the studies used for assessment of risk needs to be discussed in the risk description section of the ecological assessment.

① Comment: Monsanto stated that none of the Monsanto formulations registered in the United States for direct application to aquatic environments contain POEA-type surfactants or any surfactants that alter the aquatic toxicity profile when compared to glyphosate itself. Monsanto also suggested that rather than using a structure activity relationship approach to predict toxicity of the various surfactants used in glyphosate formulations, testing representative formulations that contain the highest concentration of a given surfactant used for direct application to water on one or two aquatic species predicted to be most sensitive to that surfactant would be more efficient.

Response: The Agency is aware that none of the Monsanto formulations registered for use in aquatic environments in the United States contain POEA-type surfactants. The Agency will be checking the formulations registered for use in aquatic environments for the listed Registrants. The Agency appreciates the suggestion from Monsanto concerning selected testing of representative formulations and will consider that suggestion when conducting the registration review for glyphosate.

Comment: Monsanto noted that for the California Red-legged Frog (CRLF) risk assessment on glyphosate, both the terrestrial invertebrate endpoint and the Level of Concern (LOC) for terrestrial invertebrates are extremely conservative. Furthermore, the LOC of 0.05 has not been through peer review and the endpoint appeared to be based on a NOAEL rather than an LD₅₀. They suggested that a new honeybee study conducted on the potassium salt (MRID 47669801) should be used for selection of a NOAEC if a NOAEC continues to be used as an endpoint.

Response: The Agency duly notes that the LOC of 0.05 for terrestrial invertebrates has not yet been through peer review. This LOC was selected as an interim measure for the endangered species litigation assessments and is not currently being used for other environmental risk assessments. The terrestrial invertebrate endpoint for the CRLF is based on the highest dose tested in a honeybee study conducted with technical glyphosate because the LD₅₀ is greater than the highest dose tested. However, the endpoint is not actually based on a NOAEL because there was 27% mortality at the highest dose tested. Normally, risk quotients (RQs) are not calculated from acute toxicity studies which report LD₅₀ or LC₅₀ values that are greater than the highest dose/concentration tested. However, for those studies with LD₅₀/LC₅₀ values that are not discrete and report some mortality, RQs are generated and then characterized as bounding estimates. That was the case with the CRLF document on glyphosate. The honeybee study conducted with the potassium salt (MRID 47669801) also reports a nondiscrete LD₅₀ with some mortality at the

① Monsanto rappelle qu'aucune formulation enregistrée aux E.U. contient du POEA pour l'application aquatique, ni aucun autre surfactant d'une toxicité pouvant altérer le milieu aquatique, mais seulement au G lui-même.

highest dose tested. The Agency will examine this study for possible use in future assessments.

Comment: Monsanto stated that the CRLF risk assessment considered only a few application rates. The discussion does not consider the wide range of application rates. It was suggested that "future risk assessments indicate the application rate in acid equivalents at which the risk quotient (RQ) equals the trigger value (LOC). It can then be inferred that any rate below this threshold value would be expected to pose minimal risk and any rate equal to or greater than this value might result in potential effects."

Response: The CRLF assessment considered all application rates in California and reported the risk estimates as exactly what Monsanto is suggesting. As an example, the following statement was provided for plants: "for terrestrial plants, the LOC is exceeded following spray drift with aerial applications at rates of 3.75 lbs/A and above and with ground applications at a rate of 7.95 lbs/A."

Comment: Monsanto provided a brief summary of their submitted threatened and endangered species assessment entitled, "The Analysis of Possible Risk to Threatened and Endangered Species Associated with Use of Glyphosate-Containing Herbicides in Roundup Ready Crop Production (Alfalfa, Canola, Corn, Cotton, Soybeans and Sugar Beets)."

Response: The Agency has not yet had the opportunity to examine the submitted risk assessment and as stated previously, will consider the assessment as part of the Registration Review for glyphosate.

Comment: The registrant stated that incorrect values were reported for the molecular weight (MW), Vapor Pressure (VP), and Henry's Constant (K_H).

Agency Response: EFED acknowledges the reported molecular weight of glyphosate is an error. EFED agrees the molecular weight of glyphosate is 169.1 grams/mole instead of 170.8 grams/mole. The proper VP and K_H for glyphosate need to be confirmed with registrant-submitted product chemistry data.

Comment: The registrant stated the exposure assessment should account for the soil binding properties of glyphosate, AMPA, and POEA. The soil partitioning coefficients of glyphosate, AMPA, and POEA indicate these compounds will not move from the target application site in the dissolved phase of runoff or bound to sediment in natural surface waters.

Agency Response: Aquatic exposure assessments are routinely based on both modeling and monitoring data. Soil:water partitioning coefficients are used in the OPP exposure models (ie, PRZM-EXAMS) to predict the partitioning of pesticide in soil and water. This assessment approach is suitable for glyphosate and AMPA because they are single compounds. In contrast, the environmental fate characteristics of polyethoxylated tallow amines (POEA) is more difficult to assess because they are not a single compound but a class of compounds with different length of the carbon chain

Proprietier of the Moby Dick Hotel and Oysterfarm, Nahcotta, Washington (Willapa Bay)

Two comments were provided by the proprietor of the Moby Dick Hotel and Oysterfarm (Fritzi Cohen) on Willapa Bay, Washington. These two responses will be summarized together.

Comment: Mrs. Cohen urges that the aquatic uses for glyphosate and its formulated products be prohibited. She specifically refers to the spraying of Spartina grass with the glyphosate formulation, Rodeo and is concerned about the potential impact of the both the formulation and any surfactants used with it on the ecosystem. In addition, she provides some history on the use of Rodeo for vegetation control in the Bay, and expresses further concern about potential synergistic effects between glyphosate and carbaryl, which has been used for many years to kill native ghost shrimp. She states that a second glyphosate formulation, Aquaneat is currently being used in combination with Polaris (an imazapyr formulation). She further states that the impact of these two formulations on the ecosystem has not been tested and that potential synergistic effects with carbaryl have not been addressed. For the past 5 years there has been no natural oyster larval set, which was abundant at one time. The Bay is low in oxygen and there have been algal blooms. She is concerned that the use of these chemicals has depleted the oxygen, possibly suffocating the fish and potentially contributing to global warming. Finally, drift of glyphosate products onto her oysterbeds was documented in 2007 and in 2009 and she has had to suspend her oyster harvests. Her business has been seriously impacted.

Response: During Registration Review, the Agency will be evaluating the potential ecological risk for all glyphosate uses, including aquatic uses. Limited ecotoxicity data have been submitted to the Agency for glyphosate formulations, both with and without surfactants, including the formulation, Rodeo. All available ecotoxicity data on currently registered formulations will be evaluated and considered during Registration Review. In addition, ecotoxicity data on both glyphosate, glyphosate formulations and surfactants from the open literature will be considered if the data are scientifically sound. The Problem Formulation for glyphosate states: "...[b]ecause the available data indicate the possibility that some formulations, even those not containing POEA can be considerably more toxic to aquatic organisms than the technical material alone, there is uncertainty associated with the risk to aquatic organisms. There are many formulated products for glyphosate and the surfactants used in these products must first be identified. Without toxicity data on specific formulations, the Agency is considering two possible approaches to addressing the toxicity of formulated products that are registered for direct application to water. The first approach is to consider structure activity relationships for the surfactants. The Agency would use the data that it does have (e.g. POEA) to predict the toxicity of surfactants with similar structure. A second approach is to request toxicity testing for a subset of the surfactants....". The Agency has asked for comment on the proposed approaches and is open to other suggestions for addressing these uncertainties.

In response to the question concerning the use of Aquaneat (glyphosate product) in combination with Polaris (imazapyr product) and/or the potential synergistic effects with the use of carbaryl in the local area, at this time, the Agency does not routinely include in its risk assessments an evaluation of mixtures external to formulated products (e.g., tank and environmental mixtures) owing to the many exposure and toxicological complexities for which there are no current peer

② Le problème de formulation⁵ du G: En raison, parce que les données valables indiquent qu'il est possible que quelques formulations y compris celles ne contenant pas de POEA peuvent être considérablement plus toxique pour les organismes aquatiques que le matériel technique (G?). Tout seul, cela est probablement avec le risque des organismes aquatiques (?). Il y a de nombreuses formulations de G et de surfactants utilisés dans les produits qui doivent en priorité identifier

reviewed evaluation models. In the case of the product formulations of active ingredients (that is, a registered product containing more than one active ingredient), each active ingredient is subject to an individual risk assessment for regulatory decision regarding the active ingredient on a particular use site. If effects data are available for a formulated product containing more than one active ingredient, they may be used qualitatively or quantitatively in accordance with the Agency's Overview Document and the Services' Evaluation Memorandum (U.S., EPA 2004; <http://www.epa.gov/espp/consultation/ecorisk-overview.pdf>).

It is noted that glyphosate, imazapyr and carbaryl have different mechanisms of action, which may or may not play a role in any synergistic effects. The Agency has no data on any potential combined effects of these three pesticides on the local ecosystem. Glyphosate is a post-emergent, systemic herbicide and is a potent and specific inhibitor of the enzyme 5-enolpyruvylshikimate 3-phosphate (ESPS) synthase. This enzyme is the sixth enzyme on the shikimate pathway and it is essential for the biosynthesis of aromatic amino acids and other aromatic compounds in algae, higher plants, bacteria and fungi. Inhibition of this enzyme leads to plant cell death. Uptake of imazapyr is primarily through the foliage and roots. It is then translocated to meristematic tissue where it inhibits acetohydroxyacid synthase (AHAS or ALS), thus, disrupting protein synthesis and interfering with cell growth and DNA synthesis. Glyphosate and imazapyr are used together because their herbicidal activity is enhanced, particularly as it relates to absorption and uptake through the roots and the ability to use the mixture prior to emergence and still have herbicidal activity. Carbaryl is a cholinesterase inhibitor that acts on animals on contact and upon ingestion by competing for binding sites on the enzyme acetylcholine esterase, thus preventing the breakdown of the neurotransmitter acetylcholine. Carbaryl is also used to thin fruit in orchards; its activity in the abscission of flower buds may be related to its structural similarity to plant auxins, such as α -naphthalene acetic acid.

Mrs. Cohen states that the Bay is low in oxygen and there have been algal blooms. She is concerned that the use of these chemicals has depleted the oxygen, possibly suffocating the fish and potentially contributing to global warming. It is true that the use of these herbicides may deplete the oxygen in the local areas where they are used, especially if their use creates considerable dead and decaying vegetation. Further testing would have to be conducted to predict the concentration levels at which adverse effects may occur. Then, modeling may possibly be used to estimate the maximum distance from the application site(s) where those effects may be still be observed.

Center for Food Safety

Comment: The Agency should expand the assessment to include numerous existing amphibian studies in the open literature.

Response: The assessment will include the existing amphibian studies from the open literature. The majority of the amphibian studies summarized and/or footnoted in the comment have already been reviewed by the Agency and were considered as part of the CRLF assessment (<http://www.epa.gov/espp/litstatus/effects/redleg-frog/#glyphosate>). Please also refer to

③ Repaire Agency: C est un post-emergent, herbicide systémique et il est potentiellement et spécifiquement un inhibiteur de l'enzyme 5-enolpyruvylshikimate 3-phosphate (ESPS) synthase. Cette enzyme est la 6^e enzyme sur le shikimate et est essentiel pour la biosynthèse de acides aminés aromatiques et autres composants aromatiques dans les algues, "higher?" plantes, bactéries et "fungi?" L'inhibition des ces enzymes et il mène à la mort des cellules végétales.

Appendix J on the same web page. Many of these studies are tabulated in the Appendix tables if they were considered to be of sufficient scientific quality to be summarized.

Comment: The Agency did not list a single study on the effects of glyphosate or its formulations on frogs or other amphibians in Tables 5 to 11 of the Ecological Risk background document.

Response: The purpose of the Problem Formulation document is to summarize the most sensitive endpoints for potential use in the quantitative assessment of risk for Registration Review. There are hundreds of ecological toxicity studies that have been conducted with glyphosate and its formulations. The intent of the Problem Formulation is not to tabulate all those studies but to provide a framework around which the ecological assessment of risk may be built. It is noted that in the absence of sufficient amphibian data, the Agency utilizes toxicity data on freshwater fish as a surrogate for aquatic-phase amphibians and on birds as a surrogate for terrestrial-phase amphibians. For glyphosate, toxicity data are available for both freshwater fish and aquatic-phase amphibians. The freshwater fish endpoints are more sensitive (e.g., more conservative). Unless new amphibian data are submitted or found that provide more sensitive endpoints for an assessment of risk, the freshwater fish data will be used as a surrogate to estimate direct risk to aquatic-phase amphibians. Use of the more conservative fish endpoints is intended to protect the more sensitive amphibian species. Currently, the Agency has not found any toxicity studies on glyphosate with terrestrial-phase amphibians. Therefore, toxicity data on birds will be used as a surrogate for the terrestrial-phase amphibians.

Comment: The Agency should expand its ecological risk assessment to include glyphosate formulations that include non-POEA surfactants.

Response: The Agency plans on including other surfactants in the assessment when there are sufficient data to allow for an assessment of risk. Risks following exposure to the technical material and to formulations will be assessed for both aquatic and terrestrial organisms following both aquatic and terrestrial applications. Please examine the CRLF assessment to see how this was done for uses registered in California <http://www.epa.gov/espp/litstatus/effects/redleg-frog/#glyphosate>. As stated previously and in the Problem Formulation, the Agency is considering two possible approaches to addressing the toxicity of formulated products that are registered for direct application to water, has asked for comment and is open to suggestions for addressing these uncertainties.

Comment: "The EPA should remove whatever internal impediments may exist to full consideration of high-quality research in the peer-reviewed literature regarding the ecological risks of glyphosate and its formulations. There is a surprising lack of references to any independent peer-reviewed scientific literature in the Ecological Risk background document...The Agency states that it consults "open literature studies"... but fails to present any evidence in the way of concrete references that it does so. EPA should not artificially limit its consultation of peer-reviewed scientific literature by overly restrictive screening procedures for "consistency", such as may be associated with acceptance into its ECOTOX database...Excessive concern for consistency should not blind the Agency to high-quality data that has been generated by independent scientists and published in peer-reviewed journals are

almost always of higher quality than registrant-conducted or commissioned studies.”

Response: The process by which the Agency screens the open literature studies is summarized in the following document:

EPA. 2004. Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs. Office of Prevention, Pesticides, and Toxic Substances. Office of Pesticide Programs. Washington, D.C. January 23, 2004. The following is a link to the document:

<http://www.epa.gov/espp/consultation/ecorisk-overview.pdf>

As an example of the type of data the Agency extracts from the open literature, the following appendix to the CRLF assessment provides the list of references for glyphosate that were found in the open literature and considered at the time when the CRLF assessment was conducted. This list also includes an explanation of OPP acceptability criteria and rejection codes for the ECOTOX data.

<http://www.epa.gov/espp/litstatus/effects/redleg-frog/glyphosate/appendix-g.pdf>

The following appendix to the CRLF provides the data table for the acceptable studies from the open literature. These were all reviewed for the CRLF assessment.

<http://www.epa.gov/espp/litstatus/effects/redleg-frog/glyphosate/appendix-h.pdf>

Comment: The Agency should make a priority of collecting full data on the surfactants contained in every glyphosate formulation, whether registered as a formulated product or not. The Agency should demand data on the specific surfactants in every glyphosate formulation that is employed in the field as a condition of FIFRA registration.

“The Agency should collect data on the ecological impacts of all glyphosate formulations and not rely on separate analyses of surfactants’ toxicity, either through collection of data from direct test of the surfactants alone, or analysis of structure-activity relationships to extrapolate from the toxicity of known surfactants to those of similar structure....When direct testing of formulations is not possible, toxicity testing of surfactants should be preferred to predictions from similarities in structure among surfactants.”

Response: The Agency thanks the Center for Food Safety for these comments and will take them into consideration during the Registration Review process. As a note, the Agency does receive acute toxicity data for mammals on all formulations.

Comment: The Agency should not limit its assessment of the ecological toxicity of glyphosate formulations to those registered for direct application to water (as suggested in IBID, p. 31).

Response: For Registration Review, the Agency will be assessing all registered applications, including non-aquatic uses. On page 31 of the Problem Formulation, anticipated data needs for

aquatic organisms were discussed because with the current data, they appear to be the most susceptible to the toxicity of formulations containing POEA. Toxicity to aquatic organisms does not imply that the Agency is only planning on assessing aquatic uses.

Comment: "EPA's review should also include further study of the toxicity of glyphosate formulations to freshwater aquatic plants, especially given the moderate to high toxicity found to duckweed and diatom, respectively (Ecological Risks, Table 6, p. 19; we note that EPA should fill in the "toxicity category" column for these two studies, with "Moderately toxic" (duckweed) and "Highly toxic" (freshwater diatom)."

Response: The Agency acknowledges the comment on aquatic plants; however, the Agency does not assign toxicity categories to either aquatic or terrestrial plants. Those categories are specifically meant for animals and cannot be interpreted in the same way for plants. The EC₅₀, EC₂₅ and EC₀₅ values for plants are not based on mortality (immobility) as the LD₅₀ and LC₅₀/EC₅₀ values are for aquatic and terrestrial animals. For glyphosate, its salts and formulations, the Agency already has received and reviewed considerable aquatic plant data and the data requirements are considered complete for aquatic plants.

Comment: The Agency should consider the impact of glyphosate on soil biota, nutrient deficiencies and plant disease.

Response: The Agency will consider this comment; however, it should be noted that the Agency does not routinely assess risk to soil biota.

Beyond Pesticides

Comment: In response to the request for comment on the approaches to addressing the toxicity of formulated products that are registered for direct application to water (structure activity versus requesting toxicity testing for a subset of the surfactants), Beyond Pesticides stated that "the Agency must utilize toxicity testing and toxicity data, which can be supplemented with SARs, in its assessment of POEA."

Response: The Agency thanks the commenter for their input.

Dr. Don M. Huber, Professor Emeritus of Plant Pathology, Purdue University

Comment: Dr. Huber expressed concerns on the residual effects of glyphosate in crop production and environmental ecology. Specifically, he provides open literature as well as circumstantial evidence to suggest glyphosate causes adverse effects to soil fertility, soil ecology and disease resistance in crops. The effect of glyphosate on soil fertility is claimed to be associated with immobilization of micronutrient metals (Fe, Mn, Zn, and Cu) through chelation with glyphosate. Additionally, he claims glyphosate is toxic to beneficial plant-microorganism symbiosis (N fixing bacteria and mycorrhizae). He also expresses concern about the effect of secondary glyphosate release from root exudation, soil accumulation, drift on the soil fertility and plant production. He also cites literature that glyphosate predisposes plants to soil borne plant

pathogens such as Pythium, Phytophthora, Rhizoctonia, and Fusarium. Dr. Huber cites literature on the resurgence of lesser known plant pathogens and some soil borne pathogens to glyphosate use.

Response: EFED appreciates Dr. Huber sharing his extensive literature citations and personal experience on the effect of glyphosate on crop production and environmental ecology. EFED does not routinely consider the secondary ecological effects from modifications of soil fertility or microbial ecology. This information will be taken into consideration in the Registration Review.

References:

U.S. EPA. 2004. Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs. Office of Prevention, Pesticides, and Toxic Substances. Office of Pesticide Programs. Washington, D.C. January 23, 2004.