Responses to Major Comments on Technical Support Document

Public Health Goal
For
Glyphosate
In Drinking Water

Prepared by

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INTRODUCTION

The following are the combined responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for Glyphosate, based on the pre-release review draft. Changes have already been made in response to these comments, and have been incorporated into the draft. For the sake of brevity, we have selected the more important or representative comments for responses. Comments that are direct quotations appear within quotation marks and paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, please visit the OEHHA Web site at www.oehha.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Summary of comments from Monsanto (received August 2006)

Comment 1: "We do not believe that published epidemiology studies are relevant to the safety assessment of exposure to glyphosate residues in drinking water. By nature and design, epidemiology is focused on exposures, usually occupational, arising through uses of pesticides, and not to oral exposure via food or water residues."

"We do not believe that exposure or potential effects arising through environmental contact are relevant to the safety assessment of human exposure to glyphosate residues in drinking water."

Response 1: OEHHA considers toxicity studies of all kinds in its review. OEHHA is aware of the limitations of the ecological and epidemiological studies described in the glyphosate PHG document. The lack of reliable exposure information, the potential for recall bias, and the presence of confounding factors were all mentioned regarding the interpretation of these studies. No change to the PHG document was made in response to this comment.

Comment 2: *The commenter criticized a report by Garry et al. (2002) who found an association between attention-deficit disorder (ADD) and use of glyphosate on three points, (a) reliability of ADD self-reports, (b) reliability of self-reports of exposure, and (c) lack of biological plausibility.*

Response 2: OEHHA is aware of the limitations of this study. As was stated in the glyphosate PHG document, a small number of subjects, exposures to multiple chemicals, and the possibility of recall bias limit the usefulness of this study.

However, OEHHA has a different view on the biological plausibility. The commenter suggested that because glyphosate has not been found to be teratogenic, neurotoxic, or a reproductive toxin, and that the systemic doses in the applicators are likely to be very low, glyphosate could not be the cause of ADD. There have been difficulties and uncertainties in extrapolating animal neurotoxicity study results to humans. Studies in laboratory animals may not be as sensitive as evaluations of results in humans. The effect of lead exposure on the intelligence of small children is an example. Negative results in several toxicological studies do not necessarily mean the association reported by Garry *et al.* must be wrong.

"Difficulties in diagnosis" has been added to the list of concerns of this study in the PHG document.

Comment 3: *The commenter faulted the methodology and findings of a study reported by Hardell et al. (2002) who found an association between glyphosate exposure and non-Hodgkin's lymphoma or hairy cell leukemia.*

Response 3: OEHHA understands the limitations of case-control studies. As stated in the glyphosate PHG document, "The data set is weakened by the fact that there were only 8 glyphosate-exposed cases, as well as the potential for recall bias in this type of study." It is important to note that OEHHA did not consider this study adequate evidence for carcinogenic potential of glyphosate. No change to the PHG document was made in response to this comment.

Comment 4: "We do not believe that direct ingestion of formulated products, whether intentional or accidental, is relevant to the safety assessment of glyphosate residues in drinking water."

Response 4: OEHHA believes these types of studies are relevant to the discussion of the toxic effects of glyphosate and should be included in the toxicological profile. Whether this type of information should be used in the development of a health-based drinking water level depends on the breadth of the toxicity database and the availability of a more suitable toxicity study. In this case, more appropriate animal data are available. No change to the PHG document was made in response to this comment.

Comment 5: "We do not believe that sporadic findings from non-standard, non-validated studies such as Daruich et al., 2001, Nakashima et al., 2002 and Walsh et al., 2000 which are not conducted according to international guidelines or in Good Laboratory Practices-compliant testing facilities represent any credible hazard to human health or the environment."

Response 5: The study by Nakashima *et al*. (2002) was not cited in the PHG document. OEHHA agrees with the commenter that the other two studies have their limitations in terms of design and reporting. Nevertheless, these two studies were published in peer reviewed scientific journals and should be included in the toxicological review. No change to the PHG document was made in response to this comment.

Additional comments from Monsanto (received August 2006)

Comment 1: "What are the criteria OEHHA is using for selecting studies to be included for its reviews and how is the quality and value of the data in these studies being assessed in evaluations of chemicals and the setting of the PHG?"

Response 1: In the development of PHGs, OEHHA considers toxicity information of all kinds but generally puts more weight on studies published in peer reviewed scientific journals or conducted by reputable institutions, such as the National Toxicology Program (NTP), funded by the federal government. Indeed, one of the critical tasks of developing PHGs is to recognize the strengths and weaknesses of the studies being reviewed and choose the most relevant and appropriate studies for human health risk assessment. No change to the PHG document was made in response to this comment.

Comment 2: *Referring to the Summary Section, page 1, the commenter said that because U.S. EPA chose the same rabbit developmental toxicity study that was used by OEHHA and applied an uncertainty factor of 100 to develop its RfD of 2 mg/kg-day, why does OEHHA need an additional factor of 10 in setting the PHG for glyphosate?*

Response 2: In the Summary Section, it was stated that an additional uncertainty factor of 10 was used to account for the severity of the endpoint (death in this case). No change to the PHG document was made in response to this comment.

Comment 3: *Referring to the Summary Section, page 1, the commenter stated,* "'The proposed value is judged to be protective of potential sensitive populations, including pregnant women and their fetuses, infants and children and the elderly.' As no susceptible subgroups have been identified we request the removal of the phrase 'potential sensitive subpopulations such as pregnant women and their fetuses and children and, the elderly.' from the sentence on pages 1 and 23 or provide a basis for including these statements that are at odds with the conclusion on subgroups as stated on page 24."

Response 3: The California Safe Drinking Water Act (HSC 116365) requires OEHHA to consider sensitive subgroups in deriving PHGs, and OEHHA considers it to be appropriate to note that such groups have been considered in the risk assessment. Because no potentially sensitive subgroups were identified, OEHHA considered the PHG value derived by using adult exposure assumptions as sufficiently protective of other age groups as well. If a sensitive subgroup were identified in the evaluation, a lower PHG value would have been developed due to the use of exposure parameters specific to infants or children and/or the use of an additional uncertainty factor. No change to the PHG document was made in response to this comment.

Comment 4: *Referring to the Introduction Section, page 2, the commenter stated,* "Glyphosate's primary mode of action is inhibiting the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSP synthase). This enzyme is found in plants not mammals including man. Please include a sentence stating that this enzyme is found in plants, microbes, and fungi but not mammals including man thereby providing a selective toxicity to plants."

Response 4: Wording similar to that suggested by the commenter has been added to page 2.

Comment 5: *Referring the Introduction Section, to page 2, the commenter stated,* "Please delete the IRIS paragraph. The toxicology data on glyphosate in the IRIS database is significantly out of date. The Oral reference dose was calculated in 1990 using the original studies conducted with glyphosate (see section on Revision History below). The chronic rat and rat multigenerational reproduction toxicology studies were repeated at much higher doses and supersede the earlier studies."

Response 5: Changes have been made to the relevant paragraph on page 2 to indicate the oral reference dose in the IRIS database was last revised in 1990.

Comment 6: *Referring to the Introduction Section, page 3, the commenter stated,* "If this document is to provide a brief summary of relevant oral and dermal toxicity studies in the context of the updated review of chemical contaminants why are studies with intraperitoneal routes of exposure, in vitro studies, reports on effects following intentional suicides and epidemiology studies included in this review? What is the relevancy of these to oral or dermal exposures to drinking water?"

Response 6: In the evaluation of toxicological properties of a chemical, OEHHA generally reviews all routes of exposure. This is particularly relevant when the chemical is a systemic toxicant and the target organs are not dependent on the route of exposure. It is important to note that while OEHHA included intraperitoneal injection studies in the review, these studies were not selected for dose-response characterization.

The last paragraph of the Introduction Section has been changed to reflect that not only oral and dermal toxicity studies were included in the review.

Comment 7: *Referring to the Chemical Profile Section, to page 2, the commenter stated,* "It should be noted that there is no commercial product called "Roundup®" in the US markets today. Roundup® represents a group of branded products."

Response 7: We note that several registered glyphosate products use the term "Roundup" in their names. The term "Roundup®" has been changed to "Roundup branded herbicides," "Roundup products," or similar wording.

Comment 8: *Referring to the Chemical Profile Section, page 3, the commenter stated,* "It is correct that glyphosate is usually formulated as a salt (isoproplyamine, potassium, ammonium) however not all salts are the same. The trimethylsulfonium salt of glyphosate (sulfosate) is very different and in fact has a different toxicity profile, it has an acute RfD while glyphosate does not, it has a different chronic RfD and is registered separately in the US and Europe. Therefore, it is inappropriate to include it in an evaluation of "glyphosate"."

Response 8: Glyphosate and sulfosate contain the same active moiety of N-(phosphonomethyl)glycine. Roundup is the isopropylamine salt of the parent acid. Sulfosate is the trimethylsulfonium salt of the same acid; it is sold under the trade name of Touchdown®. We acknowledge their difference as formulated products. In biological systems, these two salts disassociate and give the same anion. Both products would also be expected to be dissociated if found in drinking water.

The difference in acute toxicity of various formulations of glyphosate may be attributed to the difference in absorption rate or the use of different surfactants. Perspectives on the toxicity of the N-(phosphonomethyl)glycine moiety can potentially be obtained from

review of the data for both salts. No change to the PHG document was made in response to this comment.

Comment 9: *Referring to the Environmental Occurrence and Human Exposure Section, Soil, page 5, the commenter stated,* "WHO, 2005 is not the correct reference for the information on the silvicultural spraying. The selected data comes from a study by Juahiainen et al. 1991 and was discussed in the 1994 WHO Environmental Health Critera 159."

Response 9: The reference has been changed as suggested.

Comment 10: *Referring to the Environmental Occurrence and Human Exposure Section, Water*, *page 5, the commenter stated,* "Please provide the literature reference for this statement; "Inhalation of spray droplets by agricultural workers and residents living near agricultural fields can be an important exposure pathway". There is absolutely no scientific evidence to indicate that inhalation of spray droplets are an important route of exposure to glyphosate for applicators and especially not for people living near agricultural fields. To control spray drift spray droplets must be 100 microns or more in diameter and these are physically too large to enter the lungs. Particles having an aerodynamic diameter of 5 to 30 microns also would not enter the lungs and would be deposited in the nasopharyngeal region."

"Furthermore, investigators in a biomonitoring study (Acquavella et al. 2004) with a limit of detection of 1 ppb found that 40% of the farmers who applied glyphosate had no detectable levels of glyphosate in their urine. This biomonitoring study reflects all routes of exposure."

Response 10: The monitoring data reported by Acquavella *et al*. (2004) showed a majority (60%) of the farmers who participated in the study had detectable levels of glyphosate in their urine on the day of application. Farmers who did not use rubber gloves had higher geometric mean urinary concentrations than did other farmers (10 ppb vs. 2 ppb). This result shows that while the dermal route is important, other exposure routes, such as inhalation and oral, should not be overlooked. In the WHO report (2004), it was stated, "In operators applying glyphosate products, cases of eye, skin, and/or respiratory tract irritation have been reported." This information supports the statement that inhalation of spray droplets may be an important worker exposure pathway.

Drift of pesticides to residents living near agricultural fields during and after a spraying operation generally poses an inhalation exposure risk. The significance of this pathway depends on weather condition, method of spraying, and the distance between the field and the residents. The study of Acquavella *et al.* (2004) found 12% of the children had detectable glyphosate in their urine on the day of application. All but one of the children with detectable concentration had helped with the application or were present during herbicide mixing, loading, or application. While there is no evidence that all the exposure took place when the children were close to the mixing, loading, or application of glyphosate, there is at least one child whose exposure cannot be easily explained. It is possible that the child was exposed because of the drift of glyphosate sprays.

We have to be careful in interpreting the results of Acquavella *et al*. because of its small sample size, with only 48 farmers and 79 children in the study. As pointed out by the authors, the study is also limited by a potential selection bias, as 12% of those who were eligible declined to participate. The study covered only a very short period of time, and the results may not encompass the variation in exposure over a longer period of time. Under different weather conditions, there could be a change in usage of personal protective equipments and pattern of pesticide drift. Finally, a tractor and boom sprayer method was used for all of the glyphosate applications in the study, so the results are not representative of other application procedures. Given the knowledge that under the right circumstances, aerosols can stay in the air for many hours and travel long distances, it is reasonable to assume that residents near fields can be exposed as a result of glyphosate spraying.

As correctly pointed out by the commenter, particle size is an important parameter in determining how far a particle can travel in air. However, the statement "Particles having an aerodynamic diameter of 5 to 30 microns also would not enter the lungs and would be deposited in the nasopharyngeal region" is wrong. It has been estimated that approximately 10-20% of particles with aerodynamic diameter between 5 and 10 microns are deposited in the pulmonary region (ACGIH, 1983). In addition, it is important to realize that even glyphosate droplets deposited in the nasopharyngeal region are absorbed and can pose a health hazard.

No change to the PHG document was made in response to this comment.

Comment 11: *Referring to the Environmental Occurrence and Human Exposure Section, Water, page 5, the commenter stated,* "The section on water degradation is not entirely correct suggest the following paragraph as a replacement and reference the Geisy et al. 2000 review…."

Response 11: The commenter did not specify what was wrong with the text regarding degradation of glyphosate in water, and it was not clear with reference to the suggested paragraph. As a result, no change to the PHG document was made in response to this comment.

Comment 12: *Referring to the Environmental Occurrence and Human Exposure Section, Food, page 6, the commenter stated,* "As residues of glyphosate at tolerance are legally allowed to be there, have never been found to exceed the tolerances and no risk to human health has been identified why is the potential exposure to glyphosate residues implied to be from contaminated vegetation? This is misleading and appears to give the impression of some risk or harm. Please delete this sentence "Ingestion of sprayed food material or products from animals fed contaminated vegetation may lead to glyphosate exposure."

Response 12: The word "contaminated" has been changed to "treated."

Comment 13: *Referring to the Metabolism and Pharmacokinetics Section, page 6, the commenter suggested that the absorbed dose is mainly eliminated in the urine, not urine and feces.*

Response 13: This sentence has been deleted.

Comment 14: *Referring to the Toxicological Effects in Animals Section, Dermal and Ocular Effects, page 9, the commenter stated,* "Please indicate the test material used in these studies? Is it glyphosate or a formulated product? Please include the references for these studies."

Response 14: This paragraph has been revised along the lines suggested.

Comment 15: *Referring to the Toxicological Effects in Animals Section, Subchronic Effects, page 9, the commenter stated,* "The NTP study was not conducted according to international guidelines nor under good laboratory practices. The cellular alterations, hypertrophy and basophilia of the acinar cells, of the salivary glands represent an adaptive response and occur in the absence of any adverse clinical or pathological effect and, therefore, are of no adverse consequence to the animal."

Response 15: Many toxicological investigations, outside the arenas of drug development and pesticide regulation, do not follow the good laboratory practices regulations, nor the international guidelines developed for submission of foreign studies in support of American marketing of pesticides and drugs. NTP studies are conducted with a formal protocol and are subject to rigorous review. The results are widely used by the scientific and regulatory communities. Unless the commenter can give specific reasons why this particular set of data is erroneous or unreliable, OHHA sees no reason to downgrade the confidence in these NTP study results. OEHHA considers all kinds of biological effects in its health hazard evaluation, including adaptive changes, undesirable effects, and overt adverse effects. No change to the PHG document was made in response to this comment.

Comment 16: *Referring to the Toxicological Effects in Animals Section, Subchronic Effects, page 10, the commenter stated*, "Johnson and Sreebny (1982) demonstrated parotid gland enlargement was directly related to the amount of non-nutritive bulk incorporated into the diet. It is important to note that the investigators compared gland enlargement observed in response to the bulk diet with the observed responses to chronic isoproterenol treatment and found many similarities. This study clearly demonstrates that there are at least two means of inducing gland enlargement and the observed findings of NTP may be due to a non-neural mechanism."

Response 16: This line of reasoning does not explain the effect observed with glyphosate. Johnson and Sreebny (1982) found that the percent increase in parotid gland weight was proportional to the increase in bulk content of the diet; i.e., 20 or 30 percent cellulose in the diet resulted in about 20 and 30 percent increases in parotid weight after both 8 and 32 days. In contrast, in the NTP study, 5 percent glyphosate induced almost a

3-fold increase in parotid gland weight in the 14-day study. In the 13-week studies, significant cytoplasmic alterations occurred in parotid gland in a graded fashion between 0.6 and 5 percent of glyphosate in mice (see table below), and the effect was even more sensitive in the rats.

Incidence and severity score for cytoplasmic alteration of the parotid salivary gland in B6C3F1 mice in the 13-week glyphosate-dosed feed study (from NTP, 1992).

Sex	Concentration in feed (ppm)					
	0	**3,125**	**6,250**	**12,500**	**25,000**	**50,000**
Males	0/10	0/10	5/10 (1.0)*	9/10 (1.6)	10/10 (2.8)	10/10 (4.0)
Females	0/10	0/10	2/10 (1.0)	9/10 (1.3)	10/10 (2.1)	10/10 (3.1)

*Average severity score based on a scale of 1=minimal, 2=mild, 3=moderate, 4=marked.

Thus these results are completely out of the range of effects induced by bulk changes in the diets. No change to the PHG document was made in response to this comment.

Comment 17: *Referring to the Toxicological Effects in Animals Section, Chronic Effects and Carcinogenicity Studies, page 10, the commenter stated,* "As there is no evidence to indicate that glyphosate is carcinogenic nor genotoxic and regulators and scientific bodies around the world have concluded that to be the case why is this not clearly indicated in the discussion on pages 10-15? What is the purpose of discussing in great detail findings that were not considered to be related to treatment? For example, no tumors have ever been concluded to be related to treatment in any glyphosate study yet tumor after tumor is discussed in great detail."

Response 17: In this section, tumor data were presented and their biological significance discussed. The determination of the carcinogenic potential of glyphosate was presented in the Dose-Response Assessment Section. No change to the PHG document was made in response to this comment.

Comment 18: *Referring to the Toxicological Effects in Animals Section, Genetic Toxicity, page 13, the commenter stated,* "Why are only the studies indicating positive results for genotoxicity discussed in detail in section of the PHG while those showing negative results are not discussed or not even identified? We request these detailed discussions be deleted or this bias be corrected by a weight of evidence analysis and discussion."

Response 18: This section has been revised. Tables 4 and 5 are deleted.

Comment 19: *Referring to the Toxicological Effects in Animals Section, Genetic Toxicity, page 14, the commenter suggested that the genotoxic effect reported by Bolognesi et al. (1997) was related to the high-dose intraperitoneal injection and was a*

result of a secondary effect. It was suggested that these experimental conditions are not appropriate or relevant to assess genotoxicity.

Response 19: OEHHA considers toxicity studies of all kinds in its evaluation, but generally puts more weight on studies using a route of administration that is more relevant to human exposure. The PHG document pointed out that the dose used in this study was very high (2 x 150 mg/kg), and did not conclude that glyphosate is genotoxic. No change to the PHG document was made in response to this comment.

Comment 20: *Referring to the Toxicological Effects in Animals Section, Teratogenicity, page 16, the commenter stated,* "The studies by Daruich and Dallegrave were not conducted according to international guidelines or under GLP and have a number of design flaws. One of the most serious flaws with these studies are test material identification. The test material that was dosed was not glyphosate only but rather glyphosate-based formulations. While the authors attribute results to glyphosate this is completely inappropriate and not scientifically supported."

Response 20: The issue regarding the merit of non-GLP studies has been addressed earlier (see Response 15) and is not repeated here.

Dallegrave *et al*. (2003) used a Roundup formulation in their study and this information is fully disclosed in the description of the study. Furthermore, OEHHA did not attribute the observed changes to glyphosate alone. It fact, it was stated in the document, "Because Roundup and not glyphosate was the test material in this study, it is possible that the surfactant, polyoxyethyleneamine, in the commercial formulation might have contributed to the observed teratogenicity."

There is ambiguity on whether glyphosate or a commercial product containing glyphosate was used in the study reported by Daruich *et al*. (2001). OEHHA contacted the authors but did not get a response.

OEHHA reviewed toxicity studies using various commercial products of glyphosate because they can provide insights into glyphosate toxicity. It is understood that the results can be affected by other chemicals in the products. No change to the PHG document was made in response to this comment.

Comment 21: *Referring to the Toxicological Effects in Animals Section, Teratogenicity, page 16, the commenter submitted an unpublished paper by Sylvester et al. (2001) that criticizes the design and reporting of a reproductive toxicity study reported by Daruich et al. (2001). Sylvester et al. questioned the validity of the finding that exposure to glyphosate during gestation caused changes in enzyme activities in the dams and their offspring. Sylvester et al. also stated that,* "Daruich *et al*. found reduced enzyme activities in the cytosol but total cellular effects were not determined and there was no assessment of total cellular NADPH/NADP."

Response 21: OEHHA acknowledges limitations of the study, such as small sample size, uncertainties in the dosage, and that some details of the study were not reported. It is also true that the paper only analyzed the cytosol fraction of homogenized tissues. We

disagree that these concerns would nullify the observed positive associations between glyphosate exposure and the increased isocitrate dehydrogenase activities in the maternal and fetal brain. The biological significance of these enzymatic changes is not clear, however. No change to the PHG document was made in response to this comment.

Comment 22: *In a follow-up comment regarding a study by Daruich et al. (2001), Sylvester et al. (2001) suggested that short exposure duration may be a possible explanation why enzymatic activity of the "low" group was not significantly different from that of the control group.*

Response 22: The explanation is possible, however, it should be noted that the period of reduced food was long enough to cause a significant reduction in total body weight gain. The average total body weight gains in the control and the "low" groups were 92.0 g and 49.5 g, respectively ($p<0.05$). No change to the PHG document was made in response to this comment.

Comment 23: *Referring to the Toxicological Effects in Animals Section, Teratogenicity, page 16, the commenter submitted an unpublished paper by Sylvester et al. (2003) that suggests reduced food intake, and not Roundup exposure, could explain the observed skeletal alterations in fetuses reported by Dallegrave et al. (2003), and criticizes the methods and report of this study.*

Response 23: Figure 1 of the paper by Dallegrave *et al.* (2003) shows there was no difference in relative body weight gain among the control, 500 mg/kg, and 750 mg/kg groups, and Figure 2 shows there was no difference in relative food intake between the control and the 500 mg/kg group throughout the study period. Nevertheless, statistically significant increases in skeletal alterations in fetuses were observed in these two dosed groups, compared with the control. These data do not support the explanation provided by the commenter. No change to the PHG document was made in response to this comment.

Comment 24: *Referring to the Toxicological Effects in Animals Section, Teratogenicity, page 16, the commenter stated,* "What is the evidence to support the statement that it is possible that the surfactant, polyoxyethyleneamine, in the commercial formulation might have contributed to the observed teratogenicity? This appears to be pure speculation. Please provide a reference to support this statement or delete it."

Response 24: In the Discussion Section of the paper by Dallegrave *et al*. (2003), it was stated, "The developmental retardations of the skeleton reported in the present study shows that the effect of glyphosate-Roundup® was more marked than that of technical glyphosate (WHO, 1994). The higher maternal toxicity reported here in comparison to that of technical glyphosate is probably related to the presence of other components in the commercial formulation, such as the surfactant polyoxyethleneamine." No change to the PHG document was made in response to this comment.

Comment 25: *Referring to the Toxicological Effects in Animals Section, Reproductive Toxicity, page 18, the commenter submitted an unpublished paper by DeSesso et al. (1998) that criticizes the design and reporting of a reproductive toxicity study reported by Yousef et al. (1995).*

Response 25: OEHHA agrees that the study suffered from small sample size and some details of the procedure and observations were not reported. The most significant deficiency is that the administered doses were only reported as 1/100 LD_{50} and 1/10 LD_{50} of glyphosate, without specifying the value of the LD_{50}. This deficiency has been clearly stated in the PHG document. But we disagree that these concerns would nullify the observed associations between glyphosate exposure and the reduction in body weight, ejaculate volume, and sperm concentration, as well as the increase in abnormal and dead sperm. No change to the PHG document was made in response to this comment.

Comment 26: *Referring to the Toxicological Effects in Animals Section, Reproductive Toxicity, page 18, the commenter requested that the study reported by Walsh et al. (2000) be removed from this review because it showed a non-specific surfactant effect and is not appropriate to be used for assessing risks of glyphosate to humans.*

Response 26: OEHHA finds it useful to include the study because it found that although Roundup altered steroid production, glyphosate alone did not. No change to the PHG document was made in response to this comment.

Comment 27: *Referring to the Toxicological Effects in Humans Section, Case Studies and Human Clinical Studies, page 18, the commenter stated,* "As a PHG is a level of drinking water contaminant at which adverse health effects are not expected to occur from a lifetime of exposure and glyphosate has never been detected in finished drinking water we request that this section with discussion on reports of attempted suicides with concentrated formulations, accidental exposures to the trimesium salt of glyphosate which is very different than the other salts of glyphosate, and a single case report on Parkinson that has no biological plausibility be deleted or justification for their inclusion and relevancy to the PHG be given."

Response 27: OEHHA considers toxicity studies of all kinds in its evaluation, generally putting more weight on studies using a route of administration that is relevant or similar to human exposure. Thus, evaluation of human effects of glyphosate ingestion is considered relevant to evaluation of glyphosate toxicity for human risk assessment. The development of PHGs is mandated by law for regulated chemicals in drinking water, irrespective of the present frequency of detection of the contaminants in drinking water.

In this section, human cases of exposure to glyphosate-containing products (Roundup® and Touchdown®) were discussed. Clearly, exposure situations related to suicide attempts are different from environmental exposures. Nevertheless, OEHHA believes these data constitute part of the toxicological profile of the chemical.

At this time there is no known mode of action of glyphosate or its commercial products as a causative factor in Parkinson's disease. It was stated in the PHG document that it is possible that the association was coincidental. Nevertheless, this paper alerts the scientific community to this possibility and encourages future investigation. No change to the PHG document was made in response to this comment.

Comment 28: *Referring to the Toxicological Effects in Humans Section, Case Studies and Human Clinical Studies, page 18, the commenter stated,* "Please remove the following statement in the last sentence of the first paragraph or provide the reference that supports this statement; "and the toxicity of glyphosate might have been increased by the presence of surfactants."

Response 28: Please see the discussion on studies reported by Sorensen and Gregersen (1999) and Dallegrave *et al*. (2003). These two references have been added to the sentence.

Comment 29: *Referring to the Toxicological Effects in Humans Section, Case Studies and Human Clinical Studies, page 19, the commenter stated,* "Please provide the relevancy of including dermal irritation studies in volunteers in the setting of a PHG."

Response 29: In general, dermal irritation studies are not directly applicable in the development of PHGs. However, this information constitutes part of the toxicological profile of the chemical. For this reason, OEHHA prefers to keep these studies in the document. No change to the PHG document was made in response to this comment.

Comment 30: *Referring to the Toxicological Effects in Humans Section, Ecological and Epidemiologic Studies, page 19, the commenter stated,* "Regarding the study by Goldstein et al. 2002. The limited amount of discussion is very misleading…how was that 23 % determined and what does this really represent in the context of 15 years and are those systemic signs directly related to glyphosate? "

Response 30: The discussion of the paper by Goldstein *et al*. (2002) has been revised.

Comment 31: *Referring to the Toxicological Effects in Humans Section, Ecological and Epidemiologic Studies, page 20, the commenter submitted three unpublished papers by Acquavella (2001 and 2003) and Adami and Trichopoulos (1999) that are critical of the epidemiological studies discussed in the section. These unpublished papers criticize the design, methodology, analysis, and results of the studies published by Hardell et al. (2002), Arbuckle et al. (2001), and Savitz et al. (1997). The commenter requested the deletion of these epidemiological studies or the justification for their inclusion and relevancy to setting a PHG for glyphosate.*

Response 31: In the description of the three epidemiological studies, their deficiencies and weaknesses were also discussed. Many of those issues overlap with those raised by Acquavella (2001 and 2003) and Adami and Trichopoulos (1999). Despite these

limitations, OEHHA believes these peer reviewed studies are part of the toxicity database and should be retained in the PHG document. No change to the PHG document was made in response to this comment.

Comment 32: *Referring to the Risk Characterization Section, page 24, the commenter stated,* "The Yousef et al. 1994 study is poorly conducted, has many flaws and does not represent credible evidence of effects on the male reproductive system. It is suggested that based on the results of the Yousef study that further study is warranted. The definitive study has been conducted and was evaluated by the WHO in the 2004 JMPR periodic review of glyphosate. The new multigenerational rat reproduction study contained all male and female reproductive endpoints including sperm analysis and was submitted by another glyphosate manufacturer. No adverse effects on the male or female reproductive system were observed in this study. As there is no evidence of any effect on the male reproductive system in any species in any study conducted according to international guidelines and under GLP we request that this paragraph be deleted or justification given for its continued reference and its relevancy to determining a PHG for glyphosate."

Response 32: OEHHA agrees with the commenter that the reproductive study reported by Yousef *et al.* (1995) has its limitations. There were only 4 rabbits in each dose group and the dosage information was not clearly reported. Nonetheless, we do not feel we can ignore this study. It is not clear what is the "multigen rat study" mentioned by the commenter. It is also not clear if this study investigated the same biological endpoints as those in the study reported by Yousef. A negative study in rats cannot preclude the possibility of a positive finding in another species, rabbit. Further, similar findings (reduction of sperm concentrations) have been reported in rats (NTP, 1992).

Comments from Syngenta (received September 2006)

Comment 1: "Syngenta is of the view that Public Health Goals (PHG) developed for chemical containments should be based on the best available toxicological data, derived from the best available studies that conform to good laboratory and scientific practices. Some of the studies discussed in PHG for glyphosate were not conducted according to internationally accepted GLP practices and some followed scenarios that did not correspond to valid physiological systems. All these questionable studies were accorded equal weight with valid GLP compliant studies. This practice should be corrected."

Response 1: Many toxicological investigations, outside the arenas of drug development and pesticide regulation, do not follow the good laboratory practices (GLP) regulations, nor the international guidelines developed for submission of foreign studies in support of American marketing of pesticides and drugs. In the development of PHGs, OEHHA considers toxicity information of all kinds but generally puts more weight on studies published in peer reviewed scientific journals or conducted by reputable institutions, such as the National Toxicology Program (NTP), funded by the federal government. Indeed, one of the jobs of developing PHGs is to recognize the strengths and weaknesses of the

studies being reviewed and choose the most relevant and appropriate studies for human health risk assessment. No change to the PHG document was made in response to this comment.

Comment 2: "The document reviewed various mutagenicity studies, some of which had procedural flaws, and accorded the same weight of relevance to all the reviewed studies. The document, after reviewing these studies failed to explicitly provide the weight of evidence conclusion from scientists and regulatory agencies worldwide – which is that glyphosate is not mutagenic."

Response 2: The section on genetic toxicity has been revised. The first paragraph now states, "Glyphosate was mostly negative in *in vivo* and *in vitro* test systems evaluating gene mutation, chromosomal aberration and DNA damage. Using the weight-of-evidence approach, glyphosate is considered to be neither genotoxic nor clastogenic."

Comment 3: "The document summarizes the conduct and results from rabbit teratogenicity study. In this study, no adverse effects were observed in pups in the absence of severe maternal toxicity. However, this review has not made this distinction, contary to the position of other regulatory agencies word wide, including US EPA. In the absence of any teratogenic or reproductive effects, it is not clear why OEHHA needs an additional 10X uncertainty factor in setting the PHG for glyphosate."

Response 3: As stated in the dose-response assessment section, the no-observed-adverse-effect-level of 175 mg/kg-day used for the risk assessment was based on maternal toxicity, not adverse effects observed in pups. The combined uncertainty factor of 1,000 includes 10-fold for inter-species variation, 10-fold for human variability and 10-fold for the severity of the endpoint (early mortality was observed in the next higher dose group) and the short exposure duration. No change to the PHG document was made in response to this comment.

Comments from George Ghali, U.S. Environmental Protection Agency

Comment 1. "…US Environmental Protection Agency has reviewed the draft document for Glyphosate (May 2006 draft…) and found it to be scientifically sound. We generally agree with your assessment of the chronic RfD with respect to the choice of study (rabbit developmental study), the end point (mortality, diarrhea/nasal discharge), and the NOAEL (175 mg/kg/d) used in the RfD assessment. However, we would like to emphasize here that OPP used an Uncertainty Factor of 100 which is 10-fold less than what you have used. We do realize that different concerns and different policies might exist dictating this variation in the use of uncertainty factor among different agencies. For your information, OPP decided not to add the otherwise appropriate 10X to account for severity of effect/duration of exposure because the weight-of-evidence shows toxicity at much higher doses in other species (NOAELs of 500, 750, 400, and 500 mg/kg/d for the one-year dog, chronic mouse, chronic rat, and two-generation reproductive toxicity

study in rats, respectively). Thus, the use of the 175 as a point of departure was sufficiently protective of all other effects (or lack thereof) in other, chronic exposure studies."

Response 1. The 1000-fold uncertainty factor used by OEHHA includes 10-fold for inter-species variation, 10-fold for human variability and 10-fold for the severity of the endpoint (mortality) and the short exposure duration in the chosen study. The derivation of this combined uncertainty factor is consistent with the usual practices of both OEHHA and U.S. EPA. We should note that U.S. EPA's current RfD of glyphosate as listed on IRIS (U.S. EPA, 2007) remains at 0.1 mg/kg-day, which is lower than the OEHHA estimated acceptable daily dose of 0.175 mg/kg-day. The federal MCL for glyphosate, set by U.S. EPA, is 700 ppb, which is also lower than the OEHHA PHG.

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