



Glyphosate Regulatory and Toxicology Highlights

[Note – This document provides additional regulatory highlights to those included in [Part II of the Lowdown on Roundup](#). Each item starts with an exact date of the EPA memo, Federal Register Notice, or other source document, and the document's title, most recent item to the oldest. Brief summaries are provided of the important new information or action taken as a result of the document. Most source documents are in the [CEHN Healthy Kids project bibliography](#)].

4/20/1998 Glyphosate – Report of the Hazard Identification Review Committee

EPA memo provides official confirmation that the glyphosate chronic Reference Dose (cRfD) has been increased 20-fold, from 0.1 mg/kg/day to 2.0 mg/kg/day. The new cRfD is based on maternal effects in a flawed short-term rabbit developmental study done in 1980.

The No Observable Adverse Effect Level (NOAEL) in the rabbit study was 175 mg/kg/day, which the EPA divided by the standard 100-fold safety factor to produce a cRfD of 1.75 mg/kg/day, which was then rounded upward by the agency to 2.0 mg/kg/day.

The EPA Committee making the decision offers no explanation why much lower NOAELs in multiple other studies were not used, including a NOAEL of 20 mg/kg/day in a chronic feeding study using dogs, which the EPA characterized as an “excellent study.” If this NOAEL had been used to update glyphosate’s cRfD, the increase would have only been from 0.1 to 0.2 mg/kg/day.

Monsanto knew that glyphosate’s cRfD needed to be raised significantly to accommodate the increases in dietary exposure occurring as a result of the adoption of genetically engineered, glyphosate-resistant crops, and so they pushed hard throughout the 1980s and 1990s to convince EPA to change the basis – and raise the level – of the cRfD.

Despite the flow of many new toxicology studies into the EPA from the 1970s through 1990s and hundreds of studies in the open, scientific literature, the Agency still decided to base the “new” cRfD on an old (1981) and obviously flawed rabbit study. The scientific basis and justification for this highly impactful decision remains a mystery.

4/17/1998 – EPA “FQPA Safety Factor Committee” concludes that the added 10-fold safety factor called for by the FQPA is not warranted in the case of glyphosate, because maternal and developmental risks to infants are well characterized.

The EPA carried out a dietary risk assessment as part of this decision process, and reported that the TMRC (Theoretical Maximum Residue Contribution, i.e. worst-case dietary exposure) accounted for less than 3% of the newly-raised glyphosate cRfD. Tolerances on the books in 1998 would have accounted for about 30% of the old cRfD of 0.1 mg/kg/day.

If the EPA had imposed the added, 10-X FQPA safety factor to glyphosate's old cRfD, the TMRC calculated in 1998 would have exceeded the cRfD, especially for infants and children exposed to glyphosate through food, beverages, and drinking water.

Such a decision would have changed the course of EPA decision-making in the years ahead, as GE, glyphosate-resistant corn, soybeans, cotton, canola, alfalfa, and sugar beets took over the seed market.

3/17/1994 and 3/2/1994 – Metabolism Committee Meeting memos, focus on glyphosate's primary metabolite – AMPA (aminomethylphosphonic acid).

Through the early 1990s and following routine policy, EPA added together residues of glyphosate and AMPA in conducting dietary risk assessments, because ample data suggested that AMPA is at least as toxic as glyphosate. Internationally, the Food and Agriculture Organization actually considers AMPA 50% more toxic than glyphosate.

In these memos, the EPA Metabolism Committee reports that field trial residue data submitted by Monsanto shows that in GE, Roundup Ready soybean grain, ~56% of the residues remaining after a glyphosate application are AMPA, and ~28% are glyphosate.

Still, the Committee decided that "AMPA need not be regulated regardless of levels observed in foods and feed." Going forward, the EPA no longer considered AMPA residues in enforcing tolerances or conducting dietary risk assessments. In assessing dietary risk, this critical decision had roughly the same effect as about doubling glyphosate's cRfD.

1/15/1993 – HED Chapter of the Reregistration Eligibility Document (RED) for Glyphosate, Case #0178

Memo provides a summary, and the draft Hazard Evaluation Division review of glyphosate human health risks.

The summary of chronic feeding studies reports a Sprague-Dawley rat study with a NOAEL of 31 mg/kg/day – a study that which would support an cRfD of only 0.3 mg/kg/day, not 2.0 mg/kg/day as set by EPA five years later.

The chapter notes that "On August 27, 1992, the HED Reference Dose (RfD) Peer Review Committee recommended that the RfD for glyphosate be established at 2/mg/kg/day..." based

on the 1980, short-term rabbit developmental study. The proposed increase, however, had not yet been confirmed by the EPA's RfD Work Group, and so was not yet official.

About five years later, on April 20, 1998, the new cRfD was included in the summary report of the HED Hazard Identification Assessment Review Committee. It is not clear whether the higher cRfD was officially approved and in place earlier than April 20, 1998.

11/19/1991 – Glyphosate in/on Corn – Tolerance Request and “Toxicology Profile”

Monsanto had requested an increase the glyphosate tolerance in corn grain from the existing level of 0.1 ppm to 2.0 ppm – a 20-fold increase. In liver and kidney of cattle and other livestock, the tolerance would rise from 0.5 to 1.0 ppm. The tolerance would also rise to 35 ppm in corn forage and fodder.

Glyphosate's chronic Reference Dose was still 0.1 mg/kg/day, and glyphosate was classified as a Group E for carcinogenicity – “evidence of noncarcinogenicity for humans.”

The toxicology branch had no objections to raising the corn tolerances to the levels requested by Monsanto.

10/30/1991 – Second Peer Review of Glyphosate [Oncogenicity]

Critical document setting forth EPA's final decision to change the classification of glyphosate from a Group C “possible human carcinogen” to a Group E (“evidence of noncarcinogenicity for humans). Of the 18 members of the EPA-Office of Pesticide Programs “Health Effects Division Carcinogenicity Peer Review Committee,” three do not concur with the Committee's decision to change the classification. Such non-concurrence is rare.

2/3/1989 – Glyphosate in or on Soybeans – TAS Dietary Exposure Analysis

Monsanto had petitioned EPA to raise the glyphosate plus AMPA tolerance in soybean grain from the existing 6.0 ppm to 20.0 ppm. The Dietary Exposure Branch recommended in favor of approval.

With the newly raised soybean tolerance, the Tolerance Assessment System (TAS) projected that all current and proposed tolerances for glyphosate would lead to TMRC exposures of 0.39 mg/kg/day, taking up 39% of the cRfD for non-nursing infants, and 19% of the cRfD for children ages 1-6.

This lack of room to expand glyphosate uses and exposures – seven years before the planting of the first GE, glyphosate-resistant crop – was recognized by Monsanto, and EPA, as a pressing problem that no doubt triggered the multi-year effort by Monsanto to change the basis for glyphosate's chronic RfD.

9/30/1988 – Glyphosate/Roundup in/on Corn – Tolerance Request and “Free Standing Summary”

Monsanto had requested an increase in the tolerance in corn grain to 1.0 ppm, up from 0.1 ppm. They also requested tolerances of 20 ppm in both corn fodder and corn forage.

Three years later, in 1991, Monsanto revised its request, and petitioned the EPA to raise the glyphosate tolerance in corn to 2.0 ppm, instead of the 1.0 ppm sought in the 1988 petition.

By 1991, Monsanto had realized that even higher tolerances would be required to cover glyphosate residues in GE, Roundup Ready corn, hence the preemptive request to increase the corn tolerance to 2.0 ppm.

6/24/1986 – Glyphosate in/on Wheat

This key EPA memo reviews the pending Monsanto request to increase several tolerances associated with glyphosate use on wheat.

The increase was needed because of a new way farmers wanted to use Roundup in wheat fields – rope wick applicators. Rope impregnated with Roundup would be suspended from a pipe in the front or back of a tractor. The pipe would be held steady about 6” to one foot above the canopy of the wheat, low enough for the rope to come into contact with taller, fast growing weeds. The hope was that enough Roundup would move from the rope onto the weeds to kill the weeds.

The memo reports the results of a recent SAP (Scientific Advisory Panel) meeting on the “potential carcinogenicity of glyphosate.” In the SAP report of 2/24/1986, the panel concurs with EPA that “the data on renal tumors in male mice are equivocal.” The panel, however, noted problems with existing cancer feeding studies, and stated:

“...the Panel does not believe that it is possible to categorize glyphosate clearly into Group C (possible human carcinogen) or Group E (no evidence of carcinogenicity for humans)> The Panel proposes that glyphosate be categorized as Group D (not classified, [lack of good data]).”

Then the EPA memo states –

“If the Agency concurs with the SAP position, glyphosate may not be considered oncogenic in male mice. If this is the case **the Delaney Clause may not apply to food additive petitions** (H petitions, 409 tolerances) for glyphosate.”

This statement is highly significant, because under then-existing EPA policy, the agency could not approve a section 409 food additive tolerance for any pesticide known to pose oncogenic risk. This prohibition arises from the Delaney Clause, a provision in the Food, Drug, and Cosmetic Act that applies to the setting of certain pesticide tolerances for cancer-causing

pesticides. The Delaney Clause states that the FDA (or EPA) cannot approve a food additive that poses cancer risk. The FDA and EPA considered pesticide residues in processed food to be a “food additive” when the level of a pesticide in a processed food exceeds the level in the raw agricultural commodity used to make the processed food.

This was important because, as EPA considered Monsanto’s request to marginally raise the glyphosate tolerance in wheat, the agency knew that glyphosate residues on wheat grain concentrate in wheat germ and bran, which are considered processed foods.

So, the decision by the SAP to not endorse a finding of oncogenic potential, which was concurred with by the EPA, made it possible for the EPA to approve a long-list of food additive tolerances in wheat and small grains, and in the years ahead, processed products or milling fractions from corn, soybean, cotton, canola, and sugar beets.

Without the 409 food additive tolerances, Monsanto would not have been able to introduce GE-Roundup Ready crops.

2/21/1986 – Reference Doses for Oral Exposure

Printout from internal EPA system that keeps track of the RfDs established for a given pesticide. This summary for glyphosate notes the current cRfD of 0.1 ppm, based on a 1981 Bio/dynamics 3-generation rat reproduction study with a NOAEL of 10 mg/kg/day.

In a section entitled “Data Considered for Establishing the RfD,” the agency lists a NOEL of 31 mg/kg/day in a chronic rat feeding study; a NOEL of 20 mg/kg/day in a chronic feeding study in dogs (labeled an “excellent study”); a reproductive NOEL of 10 mg/kg/day in rat reproduction study (basis of existing RfD), and a NOEL of 175 mg/kg/day in a rabbit teratology study.

Over the next decade, Monsanto repeatedly asked EPA to reconsider the basis for glyphosate’s chronic RfD, and conducted a number of new studies in an effort to reduce the weight EPA placed on older studies. Several of the new studies carried out by Monsanto produced very different results in comparison to the older studies.

Over the next decade, arguments were advanced by Monsanto urging the EPA to not use the old, 3-generation rat NOEL of 10 mg/kg/day, nor the dog feeding study NOEL of 20 mg/kg/day, in setting glyphosate’s RfD. In 1998, the EPA formally accepted Monsanto’s new data, and arguments, and changed the basis of glyphosate’s chronic RfD to the 1981 rabbit teratology study, and its NOEL of 175 mg/kg/day, despite major flaws in the study noted by the EPA’s toxicologists. The flaws included limited evidence of adverse effects even at the NOEL-dose level of 175 mg/kg/day. In other similar cases, EPA has increased the safety factor used in setting the cRfD from 100 to 300, 500, or 1,000, lowering the cRfD by one-third, one-half, or 10-fold.

8/13/1986 – Roundup/Glyphosate in/on Soybeans at 20 ppm

This memo is largely identical to the 6/24/1986 memo on wheat. It reports that Monsanto had requested an increase in the soybean grain tolerance to 20 ppm from the existing level of 6 ppm.

In addition, a food additive tolerance under section 409 would have to be established for soybean hulls at 100 ppm. If the EPA had not changed its classification of glyphosate oncogenicity from “possible” to “no evidence,” this petition could not have been approved.

This memo provides a review of a recently submitted dog study that the agency characterized as an “excellent study” in an earlier memo. This study led to a NOAEL of 20 mg/kg/day, which would support a cRfD of 0.2 ppm.

3/1/1986 – Glyphosate Registration Standard Revision

Memo advances a revised Toxicology Chapter for the “Glyphosate Registration Standard.”

Review notes that AMPA residues can account for up to 28% of total glyphosate plus AMPA residues. The document states – “Since the extent of glyphosate metabolism was not adequately addressed in the rat metabolism study, the possibility exists that the AMPA metabolite could pose a hazard to humans that was not evaluated by testing the parent compound, glyphosate.”

The “Tolerance Assessment” portion of the review states that 23.7% of the 0.1 mg/kg/day glyphosate ADI/RfD is taken up by the EPA’s estimate of “worst case” dietary exposure levels.

5/7/1985 – Glyphosate in/on Wheat in Oklahoma Section 18

Addendum to an earlier memo regarding a Section 18 request to use glyphosate in conjunction with a rope wick applicator on wheat fields in Oklahoma. This memo notes the need for a Section 409 food additive tolerance for wheat bran and wheat shorts. The memo then states –

“The implication of the Delaney Clause (since glyphosate is currently considered oncogenic by the Toxicology Branch) has previously been discussed.”

Accordingly, the effort by Monsanto to change EPA’s classification of glyphosate oncogenicity can be traced back at least to the spring of 1985, and this Section 18 “Emergency Exemption” request from Oklahoma.

4/18/1985 – Glyphosate in/on Wheat Grain and Wheat Straw

This detailed memo from the Residue Chemistry Branch to the Registration Division and Toxicology Branch sets forth deficiencies in the data available to the Residue Chemistry Branch

to evaluate Monsanto's petition to increase tolerances in wheat grain and straw, and other crops, in light of use of Roundup via a rope wick applicator.

Among several problems, the Residue Chemistry Branch expressed the view that Monsanto had not petitioned for a sufficient large increase in a number of tolerances, and that more data from field trials would be required to support the request.

The memo includes a table showing the "Concentration Factors" (CFs) for glyphosate residues in wheat grain before milling, wheat bran, flour, and wheat shorts. An application rate of 0.38 pound of glyphosate per acre was associated with a Concentration Factor of 2.34 in wheat bran (i.e., the residue level in wheat bran was 1.66 ppm, compared to 0.71 ppm in the grain).

While glyphosate concentrates in bran, its level decreases in flour, down to 0.14 ppm, for a CF of 0.2.

The EPA reports a CF of 1.69 in wheat shorts, as a result of the increase in residues to 1.20 ppm in wheat shorts, from 0.71 in wheat grain.

4/3/1985 – Glyphosate Mouse Oncogenicity Study

This Toxicology Branch memo reports the EPA's conclusion that "Glyphosate was oncogenic in male mice causing renal tubule adenomas, a rare tumor, in a dose-related manner."

Henceforth, and until EPA changed its determination some six years later, the EPA regarded glyphosate as a possible carcinogen, and the Delaney Clause blocked any changes in glyphosate use patterns that would require approval of a Section 409 food additive tolerance.

The use of Roundup in association with GE, herbicide-resistant crop technology would not be possible as long as EPA classified glyphosate as a possible carcinogen. This is the primary reason why Monsanto pushed so hard over the coming decade to convince EPA to downgrade its classification of glyphosate oncogenicity.

3/4/1985 – Consensus Review of Glyphosate

A group of experts in the Toxicology Branch "met to evaluate and discuss the data base on glyphosate, and in particular the potential oncogenic response of glyphosate."

Their review included assessment of the data and arguments advanced by Monsanto in a February 2, 1985 letter in which the company attempted to rebut the significance of the renal tubule tumors in mice. The arguments set forth in this 1985 letter have resurfaced in Monsanto's multiple responses to the 2015 decision by the International Agency for research on Cancer to reclassify glyphosate as a "**probable human carcinogen.**"

The Toxicology Branch expert committee classifies glyphosate as a Group C carcinogen (possible human carcinogen) based on the rare renal tumors.

2/9/1982 – Lifetime Feeding Study in Rats with Glyphosate

Memo sets forth the Toxicology Branch's review of a 1981 study conducted by Bio/dynamics for Monsanto. The NOEL for chronic toxicity was reported as 3.0 mg/kg/day. Had EPA used this study and NOEL to establish glyphosate's chronic Reference Dose, the level would have been set at 0.03 mg/kg/day, one-third of the 0.1 level in place from the early 1980s through 1998.

Monsanto persuaded the EPA not to rely on this study and NOEL because of deficiencies in the Bio/dynamic study. In addition, Monsanto pledged to redo the study. The results of the subsequent study did not identify such a low NOEL, and were used for years to support the 0.1 mg/kg/day cRfD.

11/13/1979 – Glyphosate "Free Standing" Summary of PP#9F2162 [Stone Fruit Tolerance Petition]

Memo provides an overview of the existing toxicology data base on glyphosate, and notes several data gaps and studies that must be repeated. The list of flawed studies that had to be repeated would greatly expand two years later, as a result of the scandal involving IBT testing laboratory. Following a routine EPA audit, most of the studies conducted by IBT for a number of pesticide manufacturers were found to be of very poor quality or fraudulent.

This memo sets forth the basis of the first glyphosate cRfD, called back then an ADI (Acceptable Daily Intake). The EPA based this first ADI/cRfD on a 2-year rat feeding study, with a NOEL of 5 mg/kg/day.

The ADI/cRfD was set at 0.05 mg/kg/day, the lowest level in the history of EPA's assessment of glyphosate toxicity. The current RfD is 2 mg/kg/day, a level 40-times higher than EPA's initial judgement in 1979.