March 5, 2013

TESTIMONY IN SUPPORT OF CT HB 6527, An Act Concerning Genetically Engineered Baby Food

Submitted by:
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2 Windsor Court
Farmington

My name is Diana Reeves and I am a mother of 3, aged 18 to 25. My husband, my two daughters and I suffer from autoimmune disease and food allergies. We were all diagnosed around the same time. My youngest daughter was 14 when diagnosed. A freshman in college now, her food must be prepared separately, in an isolated area of the basement in the dining hall. Life is complicated for us. We can't eat out. I can no longer read a newspaper because every time I touch the GMO soy ink, I develop a blistery rash on my face. My children have grown up eating GMOs without my knowledge or consent. I have been reading studies that link GMOs and the chemicals they are sprayed with to a very long and very disturbing list of health problems, including autoimmune disease. Had I known then what I know now, I would have fed my family very differently.

I would like to share a ~~couple of~~ few things I've learned with you.

There has never been an independent, long term safety test done on any of the genetically modified foods in our food supply.

GMO Bt corn, which is being used in our baby formulas, is an EPA Registered Pesticide. It kills insects when they bite into it. Think about it - food shouldn't kill. This is not something I would consider feeding a vulnerable baby. If this corn were on the shelf at Home Depot, you would see the pesticide registration numbers on the label. I've attached the EPA pesticide registration information to this testimony. Unfortunately, the EPA has no jurisdiction over food labeling so new mothers are unknowingly feeding their babies toxic pesticides.

With the introduction of GMO soy, Monsanto successfully petitioned the FDA to increase the allowable level of their chemical herbicide on soy. Glyphosate, the active ingredient in their herbicide, RoundUp, was increased to a level three times higher than the level that was previously determined to be safe. Glyphosate is systemically absorbed by the plant and does not wash off. Numerous lab studies have shown that glyphosate is genotoxic, endocrine disrupting, neurotoxic, and a carcinogen. Without a label, new mothers are unknowingly feeding glyphosate to their babies in soy-based formulas.

The chemical companies that are genetically altering and patenting our food will

tell you that America has been eating GMOs for almost 20 years and we are fine. But doctors now say that this is the first generation of children that are sicker than their parents. America is not fine.

Babies are our future. Mothers need to know if a product contains GMOs so they can have the freedom to choose what they feed their babies. Please vote yes on HB 6527 to label genetically engineered baby food. Without labeling, there is no accountability. Thank you.

Reference links:

http://www.co.lake.ca.us/Assets/BOS/GE+Crops+Committee/6.+GM+Crops+and+Pesticide+Use.pdf

http://www.national-toxic-encephalopathy-foundation.org/roundup.pdf

http://www.epa.gov/oppbppd1/biopesticides/pips/smartstax-factsheet.pdf

United States
Environmental Protection
Agency

Office of Prevention,
Pesticides
and Toxic Substances
(7501P)

Pesticide Fact Sheet

Name of Plant-Incorported Protectant(s):

Bacillus thuringiensis Cry 1A.105 protein and the genetic material necessary (vector PV-ZMIR245) for its production in corn event MON 89034

Bacillus thuringiensis Cry2Ab2 protein and the genetic material necessary (vector PV-ZMIR245) for its production in corn event MON 89034

Bacillus thuringiensis Cry1F protein and the genetic material necessary (vector PHP8999) for its production in corn event TC1507

Bacillus thuringiensis Cry3Bb1 protein and the genetic material necessary (vector PV-ZMIR39) for its production in corn event MON 88017

Bacillus thuringiensis Cry34Ab1 protein and the genetic material necessary (vector PHP17662) for its production in corn event DAS-59122-7

Bacillus thuringiensis Cry35Ab1 protein and the genetic material necessary (vector PHP 17662) for its production in corn event DAS-59122-7

OECD Unique Identifier: MON-89Ø34-3 x DAS- Ø15Ø7-1 x MON-88Ø17-3 x DAS-59122-7)

Reason for Issuance: Updated Expiration Date and Additional Terms and Conditions

Date Issued: November 29, 2011

I. Description of the Plant-Incorporated Protectant

- **Pesticide Name:** MON 89034 x TC1507 x MON 88017 x DAS-59122-7
- **Date Registered:** July 20, 2009
- **Registration Numbers:** 524-581 & 68467-7

- **Trade and Other Names:** MON 89034 x TC1507 x MON 88017 x DAS-59122-7 Insect Protected, Herbicide-Tolerant Corn, Genuity™SmartStax™, SmartStax™

- **OPP Chemical Codes: 006490, 006481, 006502, 006515, 006514**

- **Basic Manufacturers:** Monsanto Company
800 North Lindbergh Blvd
St. Louis, MO 63167

  Mycogen Seeds c/o Dow AgroSciences LLC
9330 Zionsville Road
Indianapolis, Indiana 46268-1054

- **Type of Pesticide: Plant-Incorporated Protectant (PIP)**

- **Uses: Field Corn**

- **Target Pest(s):** European corn borer (ECB)
Southwestern corn borer (SWCB)
Southern cornstalk borer (SCSB)
Corn earworm (CEW)
Fall armyworm (FAW)
Stalk borer
Lesser corn stalk borer
Sugarcane borer (SCB)
Western bean cutworm (WBC)
Black cutworm
Western corn rootworm (WCRW)
Northern corn rootworm (NCRW)
Mexican corn rootworm (MCRW)

II. Summary

EPA has conditionally registered MON 89034 x TC1507 x MON 88017 x DAS-59122-7, "SmartStax,", a new bioengineered corn seed product containing genes for two Bt PIPs active against corn rootworm (CRW and three Bt PIPs to control different corn borer pests.. After reviewing all pertinent data, the Agency has concluded that a lower CRW refuge of 5% is scientifically justified for SmartStax corn and will further reduce the use of conventional insecticides.

EPA has approved bioengineered "Bt corn" to control corn rootworm (CRW) since 2003. The use of such Bt corn in the U.S. has reduced conventional insecticide use for CRW by more than 75%.

Bt corn products for CRW could lose their effectiveness due to the development of insect resistance. To mitigate this risk, EPA currently requires the use of an external structured 20%

refuge of non-Bt corn. Refuges produce Bt susceptible insects to dilute any resistance genes in the pest population.

Monsanto and Dow have developed a new Bt corn product (SmartStax) with two Bt toxins (Cry34Ab1/Cry35Ab1 and Cry3Bb1) active against CRW. The use of multiple toxins against the same pest is termed a "pyramid."

SmartStax also contains three Bt PIPs to control different corn borer pests. (Corn borers have separate refuge requirements.)

EPA has previously approved a 5% refuge for corn borer pests where the corn earworm is not a significant pest and a 20% combined refuge in cotton growing regions where the corn earworm is a significant pest. The reduced CRW refuge could result in further reduction in conventional insecticide use, increased crop yields for growers, and increased grower compliance with refuge requirements.

EPA has approved a combined 5% refuge for corn rootworm and lepidopteran pests where the corn earworm is not a significant pest and a 20% combined refuge in cotton growing regions where the corn earworm is a significant pest.

III. Science Assessment

Product Characterization and Human Health Assessment

Current tolerance exemptions in 40 CFR Part 174 applicable to_MON 89034 × TC1507 × MON 88017 × DAS-59122-7.

§ 174.502 Bacillus thuringiensisCry1A.105 protein; exemption from the requirement of a tolerance.

(a) Residues of *Bacillus thuringiensis* Cry1A.105 protein in or on the food and feed commodities of corn; corn, field, flour; corn, field, forage; corn, field, grain; corn, field, grits; corn, field, meal; corn, field, refined oil; corn, field, stover; corn, sweet, forage; corn, sweet, kernel plus cob with husk removed; corn, sweet, stover; corn, pop, grain and corn, pop, stover are exempt from the requirement of a tolerance when the *Bacillus thuringiensis* Cry1A.105 protein is used as a plant-incorporated protectant in these food and feed corn commodities.

§ 174.506 Bacillus thuringiensis Cry34Ab1 and Cry35Ab1 proteins in corn; exemption from the requirement of a tolerance.

Residues of *Bacillus thuringiensis* Cry34Ab1 and Cry35Ab1 proteins in corn are exempted from the requirement of a tolerance when used as plant-incorporated protectants in the food and feed commodities of corn; corn, field; corn, sweet; and corn, pop.

§ 174.507 Nucleic acids that are part of a plant-incorporated protectant; exemption from the requirement of a tolerance.

Residues of nucleic acids that are part of a plant-incorporated protectant are exempt from the requirement of a tolerance.

§ 174.518 Bacillus thuringiensis Cry3Bb1 protein in corn; exemption from the requirement of a tolerance.

Residues of *Bacillus thuringiensis* Cry3Bb1 protein in corn are exempt from the requirement of a tolerance when used as plant-incorporated protectants in the food and feed commodities of corn; corn, field; corn, sweet; and corn, pop.

§ 174.519 Bacillus thuringiensis Cry2Ab2 protein in corn and cotton; exemption from the requirement of a tolerance.

Residues of *Bacillus thuringiensis* Cry2Ab2 protein in or on corn or cotton are exempt from the requirement of a tolerance when used as a plant–incorporated protectant in the food and feed commodities of corn; corn, field; corn, sweet; corn, pop; and cotton seed, cotton oil, cotton meal, cotton hay, cotton hulls, cotton forage, and cotton gin byproducts.

§ 174.520 Bacillus thuringiensis Cry1F protein in corn; exemption from the requirement of a tolerance.

Residues of *Bacillus thuringiensis* Cry1F protein in corn are exempt from the requirement of a tolerance when used as plant-incorporated protectants in the food and feed commodities of corn; corn, field; corn, sweet; and corn, pop.

§ 174.523 CP4 Enolpyruvylshikimate-3-phosphate (CP4 EPSPS) synthase in all plants; exemption from the requirement of a tolerance.

Residues of the CP4 Enolpyruvylshikimate-3-phosphate (CP4 EPSPS) synthase enzyme in all plants are exempt from the requirement of a tolerance when used as plant-incorporated protectant inert ingredients in all food commodities.

§ 174.522 Phosphinothricin Acetyltransferase (PAT); exemption from the requirement of a tolerance.

Residues of the Phosphinothricin Acetyltransferase (PAT) enzyme are exempt from the requirement of a tolerance when used as plant-incorporated protectant inert ingredients in all food commodities.

Southern Blot Analysis

Southern blot analysis confirmed in the combined trait corn product MON 89034 x TC1507 x MON 88017 x DAS-59122-7 the presence of sequences identical to sequences derived from MON 89034 and MON 88017.Hybridization patterns for the combined trait product were identical to those of the parental lines with *cry1F*, *cry34Ab1*, *cry35Ab1*, and the *pat* gene probes indicating that the TC1507 and DAS-59122-7 insertions were unaffected by combining with MON 89034 and MON 88017 through conventional breeding.

Expression Levels

MON 89034 x TC1507 x MON 88017 x DAS-59122-7 is a combined trait corn that produces lepidopteran-active and coleopteran-active *Bacillus thuringiensis* (*Bt*) proteins, as well as the 5-enolpyruvylshikimate-3-phosphate synthase protein from *Agrobacterium* sp. strain CP4 (CP4 EPSPS) to confer tolerance to glyphosate herbicides and PAT to confer tolerance to glufosinate herbicides. The levels of the lepidopteran-active Cry1A.105, Cry2Ab2, Cry3Bb1 proteins and the CP4 EPSPS protein were determined in tissues from MON 89034 x TC1507 x MON 88017 x DAS-59122-7 plants grown at five US field sites in 2006. The test also included a conventional corn as a negative control and MON 89034 and MON 88017 corns as positive controls. Leaf, root, and whole plant samples were collected over the growing season, as well as pollen and grain samples at the appropriate times. The samples were extracted and analyzed using enzyme-linked immunosorbent assays. The levels of the Cry1A.105, Cry2Ab2, Cry3Bb1, and CP4 EPSPS proteins in MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn were comparable to those in the appropriate MON 88017 or MON 89034 positive control.

The levels of the coleopteran-active *Bacillus thuringiensis* (*Bt*) proteins Cry34Ab1, Cry35Ab1, and Cry1F, and the PAT protein were determined in tissues from MON 89034 x TC1507 x MON 88017 x DAS-59122-7 plants grown at five US field sites in 2006. The test also included a conventional corn as a negative control and TC1507 and DAS-59122-7 parental event corn as positive controls. Leaf, root, and whole plant samples were collected over the growing season, as well as pollen and grain samples at the appropriate times. The samples were extracted and analyzed using enzyme-linked immunosorbent assays (ELISA). The results indicate that the levels of Cry34Ab1, Cry35Ab1, and Cry1F in MON 89034 x TC1507 x MON 88017 x DAS-59122-7 were comparable to the levels produced in the appropriate TC1507 or DAS-59122-7 control corn. The level of PAT in MON 89034 x TC1507 x MON 88017 x DAS-59122-7 was higher in the combined trait products compared to TC1507 and DAS-59122-7, likely due to the presence of multiple copies of the *pat* gene in the stacks (one from each of the DAS parent lines).

Environmental Assessment

At present, the Agency has not identified any significant adverse effects of the Cry1A.105, Cry2Ab2, Cry1F, Cry3Bb1, or Cry34Ab1/35Ab1 proteins on the abundance of non-target organisms in any field population, whether expressed individually or as MON 89034 x TC1507 x

MON 88017 x DAS-59122-7 combined PIP corn product. The potential for synergistic effects has been evaluated and the data that were reviewed for the individual parental events can be bridged to support the Sec. 3 registration of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 combined PIP corn product.

It is unlikely that direct or indirect harmful effects to non-target organisms, including federally-listed threatened or endangered species, would result from the insecticidal proteins Cry1A.105, Cry2Ab2, Cry1F, Cry3Bb1, or Cry34/35Ab as a result of the proposed Sec. 3 registration. The Agency anticipates that for full commercial cultivation, no hazard will result to the environment.

Event MON 89034 produces the Cry1A.105 and Cry2Ab2 Bt proteins, and Event TC1507 produces Cry1F. These proteins are intended to control or suppress several lepidopteran pests of corn, including European corn borer (ECB, *Ostrinia nubilalis*), corn earworm (CEW, *Helicoverpa zea*), fall army worm (FAW, *Spodoptera frugiperda*), and black cutworm (BCW, *Agrotis ipsilon*). MON 88017 produces the Cry3Bb1 protein, and Event DAS-59122-7 produces the Cry34Ab1 and Cry35Ab1 proteins. These two events provide additional control for coleopteran pests, particularly corn rootworm pests (*Diabrotica* spp.).

It has been determined that each individual event has protein expression levels that are comparable to the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn hybrid (Kough, 2009). Therefore, the margins of exposure that were previously determined for the insecticidal proteins in the individual events are applicable for the risk assessment of these proteins in the stacked hybrid. Additionally, no synergistic or antagonistic effects were observed in several combinations of the individual events in MON 89034 x TC1507 x MON 88017 x DAS-59122-7, as well as the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 hybrid itself. As a result, the Agency concludes that there is no indication of synergistic effects or increased levels of protein expressed in the combined PIP product, so the environmental risk assessment for the single PIP lines are applicable to the assessment of MON 89034 x TC1507 x MON 88017 x DAS-59122-7.

As a result, the environmental risk assessment of the individual events, as well as an additional study submitted on the toxicity of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 to a non-target insect, the Agency concludes that there will be no unreasonable adverse effects to the environment, including endangered species, by MON 89034 x TC1507 x MON 88017 x DAS-59122-7 combined trait corn.

Insect Resistance Management

1) Overall, Monsanto/Dow have provided sufficient scientific justification to support a reduced corn rootworm (CRW) refuge of 5% for SmartStax Bt corn. Data reviewed by BPPD include studies on dose for CRW, cross resistance between the Cry3Bb1 and Cry34Ab1/35Ab1 toxins, and simulation modeling to predict potential resistance evolution. However, BPPD notes that there is still uncertainty regarding the true CRW dose expressed by SmartStax (and its single trait

components) and worst case simulation modeling (as described in the conclusions below). Therefore, additional data have been required to be generated (as described below) to verify and further buttress the current data supporting lower refuge. BPPD intends to conduct a post-registration assessment of the lower refuge within several years of approval once any new data have been submitted and reviewed.

2) Monsanto has previously provided data to support a 5% refuge for lepidopteran target pests of SmartStax corn.

3) Given that SmartStax will likely have different refuge requirements for Lepidoptera and CRW than other registered Bt corn products, BPPD has required that Monsanto/Dow submit a revised compliance plan. This strategy should be specific for SmartStax and the new refuge requirements. Compliance is an area of ongoing concern -- recent data have shown that refuge compliance for Bt corn has fallen in recent years.

4) Existing programs for resistance monitoring and remedial action that were established for MON 89034 (Cry1A.105 and Cry2Ab2), MON 88017 (Cry3Bb1), and Herculex Xtra (Cry1F and Cry34Ab1/35Ab1) should be applicable to SmartStax corn. In light of lower required structured Bt corn structured refuge for SmartStax, BPPD has required that the CRW resistance monitoring program be expanded (i.e. with additional sampling and collection sites or improved monitoring techniques). Also, a revised definition of "resistance" may be needed for the CRW monitoring and remedial action plans based on recent research and selection experiments (Lefko et al. 2008; Meihls et al. 2008).

Conclusions Regarding Dose, Resistance Allele Frequency, and Modeling Data

5) BPPD agrees with Monsanto/Dow that the methodology used to calculate dose for SmartStax (developed in Storer et al. 2006 and used in Hucakaba and Storer 2008) is a reasonable approach to addressing dose for CRW. There is some conflicting evidence about the effect of density dependent mortality on dose calculations; BPPD agrees with Monsanto/Dow's use of the data from the Huckaba and Storer (2008) study that was not adjusted for density dependent effects. These more conservative dose estimates (96.17 - 99.96% for Cry3Bb1, 94.20 - 99.18% for Cry34/35, and 98.22 - 99.97% for Cry3Bb1 + Cry34/35 pyramid) were used in a revised model simulation.

6) Although Monsanto/Dow have used the best available dose estimates for CRW, BPPD believes that there is still uncertainty on dose in both the methodology and interpretation of available studies. This is largely due to the biology of CRW -- assessing larval response and behavior in a subterranean environment is difficult and confounding factors such as density-dependent (or independent) mortality must be considered. Storer et al. (2006) is probably the best current approach to evaluating dose, but BPPD notes that limited data have been developed using this technique (e.g. only one year with six locations of data were developed for Cry3Bb1).

Other *Diabrotica* spp. may also need to be investigated: data previously submitted for northern corn rootworm revealed mortality as low as 92.8% on Cry34/35 .

7) To address the uncertainty regarding CRW dose and buttress the dose assumptions used in the models, BPPD has required that Monsanto/Dow provide additional dose data (using the methods of Storer et al. 2006) for Cry3Bb1 and Cry34Ab1/35Ab1. Further dose studies could also be conducted with varying egg infestation levels (above and below egg levels expected to trigger density-dependent mortality) to tease out any egg density effects. New techniques to assess CRW dose may need to be pursued as well, if Monsanto/Dow or academic researchers can develop such approaches.

8) Monsanto/Dow conducted modeling simulations to investigate the effect of initial resistance allele frequency (RAF). The results from these simulations with a pyramid showed that the initial RAF was insensitive in the model -- the final RAF did not increase significantly from the initial frequency after 10 generations of selection (regardless of the starting value). Nevertheless, BPPD is still concerned that resistance alleles for CRW-targeted Bt traits may be relatively common in the field based on published CRW selection studies (Lefko et al. 2008; Meihls et al. 2008). Monsanto/Dow's default assumption of an initial RAF of 0.001. This may be suitable for other pests (e.g. Lepidoptera), but BPPD must consider the possibility that actual RAF for CRW is higher (perhaps close to 0.01). To further investigate this issue, BPPD recommends resistance selection experiments to further characterize putative resistance alleles and frequency of occurrence in CRW populations.

9) As with Monsanto/Dow's previous modeling, revised simulation modeling conducted with the lower dose estimates (described in #5 above) showed that resistance did not evolve to a pyramid with a 5% refuge, while single trait PIPs with a 20% refuge developed resistance in < 10 generations. An initial resistance allele frequency of 0.001 was used in the model; as discussed in #8 above, BPPD is concerned that resistance alleles may be more common among CRW in natural populations. However, BPPD notes that all modeling reviewed to date, including models submitted by Monsanto/Dow and published by independent researchers (Roush 1998; Zhao et al. 2003; Gould et al. 2006; Onstad 2009 - draft), strongly suggest that pyramided PIPs are superior to the current single trait CRW products and can justify a lower refuge for the SmartStax pyramid.

10) BPPD has required that new model simulations be conducted to incorporate new data (i.e. from studies conducted under #7 and 8 above) or using possible "worst case" parameters. Although Monsanto/Dow's new model simulations have been more conservative than previous runs, BPPD remains concerned that "worst case" scenarios for SmartStax have not yet been fully investigated. CRW-protected corn is highly adopted in some areas with heavy infestations so that intense selection pressure for resistance can be expected. In light of this, and the large proposed reduction in minimum refuge (from 20% to 5%; a 75% total reduction), BPPD believes that worst case analyses are warranted to help determine the potential for resistance. In

particular, model parameters for dose and initial resistance allele frequency could be adjusted to include more conservative estimates (e.g. dose ranges < 94% and RAF > 0.001).

Gould, F., M. B. Cohen, J. S. Bentur, G. C. Kennedy, and J. Van Duyn. 2006. Impact of small fitness costs on pest adaptation to crop varieties with multiple toxins: a heuristic model. J. Econ. Entomol. 99: 2091-2099.

Lefko, S.A. et al., 2008. Characterizing laboratory colonies of western corn rootworm (Coleoptera: Chrysomelidae) selected for survival on maize containing event DAS 59122-7. J. Appl. Entomol. 132: 189-204.

Meihls, L., M. Hidgon, B. Siegfried, N. Miller, T. Sappington, M. Ellersieck, T. Spencer, and B. Hibbard, 2008. Increased survival of western corn rootworm on transgenic corn within three generations of on-plant greenhouse selection. Proc. Nat. Acad. Sci. 105 (49): 19177-19182.

Onstad, D., 2009 (draft). Modeling Evolution of *Diabrotica virgifera virgifera* (Coleoptera: Chrysomelidae) to Transgenic Corn with Two Insecticidal Traits. J. Econ Entomol. Draft - to be submitted in 2009.

Roush, R.T., 1998. Two toxin strategies for management of insecticidal transgenic crops: pyramiding succeed where pesticide mixtures have not? Phil. Trans. R. Soc. Lond. 353:1777-1786.

Zhao, J., J. Cao, Y. Li, H. Collins, R. Roush, E. Earle, and A. Shelton, 2003. Transgenic plants expressing two *Bacillus thuringiensis* toxins delay insect resistance evolution. Nature Biotechnology. 21: 1493-1497.

IV. Terms and Conditions of the Registration

1) The subject registration will automatically expire on midnight November 30, 2013.

2) The subject registration will be limited to MON 89034 x TC1507 x MON 88017 x DAS-59122-7 in field corn.

3) Submit the following data in the time frames listed:

OPPTS Guideline/ Study Type	Required Data	Due Date
Insect Resistance Management	To address the uncertainty regarding CRW dose and buttress the dose assumptions used in the models, provide additional dose data (using the methods of Storer et al. 2006) for Cry3Bb1 and Cry34Ab1/35Ab1. Further dose studies could also be conducted with varying egg infestation	Report Due 11/30/2010

OPPTS Guideline/ Study Type	Required Data	Due Date
	levels (above and below egg levels expected to trigger density-dependent mortality) to tease out any egg density effects. New techniques to assess CRW dose may need to be pursued as well, if Monsanto/Dow or academic researchers can develop such approaches.	
Insect Resistance Management	Monsanto/Dow conducted modeling simulations to investigate the effect of initial resistance allele frequency (RAF). The results from these simulations with a pyramid showed that the initial RAF was insensitive in the model -- the final RAF did not increase significantly from the initial frequency after 10 generations of selection (regardless of the starting value). Nevertheless, BPPD is still concerned that resistance alleles for CRW-targeted Bt traits may be relatively common in the field based on published CRW selection studies (Lefko et al. 2008; Meihls et al. 2008). Monsanto/Dow's modeling has assumed an initial RAF of 0.001. This may be suitable for other pests (e.g. lepidoptera), but BPPD must consider the possibility that actual RAF for CRW is higher (perhaps close to 0.01). To further investigate this issue, resistance selection experiments must be conducted to further characterize the potential for resistance alleles and frequency of occurrence in CRW populations.	Annually First Report Due 11/30/2010
Insect Resistance Management	New model simulations must be conducted to incorporate new data (i.e. from studies conducted under items above) or using possible "worst case" parameters. Although Monsanto/Dow's new model simulations have been more conservative than previous runs, BPPD remains concerned that "worst case" scenarios for SmartStax have not yet been fully investigated. CRW-protected corn is highly adopted in some areas with heavy infestations so that intense selection pressure for resistance can be expected. In light of this, and the large proposed reduction in refuge (from 20% to 5%; a 75% total reduction), BPPD believes that worst case analyses are warranted to help determine the potential for resistance. In particular, model parameters for dose and initial resistance allele frequency could be adjusted to include more conservative estimates (e.g. dose ranges < 94% and RAF > 0.001).	Annually First Report Due 11/30/2010

4) Submit or cite all data required to support the Herculex Xtra and the MON 89034 x MON 88017 stacked plant-incorporated protectant products within the timeframes required by the terms and conditions of EPA Registration Numbers 68467-6 and 524-576.

5) Do the following Insect Resistance Management Program for MON 89034 x TC1507 x MON 88017 x DAS-59122-7.

The required IRM program for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn must have the following elements:

Requirements relating to creation of a non-*Bt* corn refuge in conjunction with the planting of any acreage of MON 89034 x TC1507 x MON 88017 x DAS-59122-7corn;
Requirements for Monsanto/Dow to prepare and require MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn users to sign "grower agreements," which impose binding contractual obligations on the grower to comply with the refuge requirements;
Requirements regarding programs to educate growers about IRM requirements;
Requirements regarding programs to evaluate and promote growers' compliance with IRM requirements;
Requirements regarding programs to evaluate whether there are statistically significant and biologically relevant changes in target insect susceptibility to Cry1A.105, Cry2Ab2, Cry3Bb1, Cry1F and Cry34Ab1/Cry35Ab1 proteins in the target insects;
Requirements regarding a "remedial action plan," which contains measures Monsanto/Dow would take in the event that any field-relevant insect resistance was detected as well as to report on activity under the plan to EPA;

Annual reports on units sold by state (units sold by county level will be made available to the Agency upon request), IRM grower agreements results, and the compliance assurance program including the educational program on or before January 31st each year, beginning in 2011.

a) Refuge Requirements for MON 89034 x TC1507 x MON 88017 x DAS-59122-7

These refuge requirements do not apply to seed propagation of inbred and hybrid corn seed up to a total of 20,000 acres per county and up to a combined U.S. total of 250,000 acres per PIP active ingredient per registrant per year. Grower agreements (also known as stewardship agreements) will specify that growers must adhere to the following refuge requirements as described in the grower guide/product use guide and/or in supplements to the grower guide/product use guide.

A common refuge must be planted for both corn borers and corn rootworms. The refuge must be planted with corn hybrids that do not contain Bt technologies for the control of corn rootworms or corn borers. The refuge and MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn should be sown on the same day, or with the shortest window possible between planting dates to ensure that corn root development is similar among varieties. If the refuge is planted on rotated ground, then the MON 89034 x TC1507 x MON88017 x DAS-59122-7 corn must also be planted on rotated ground. If the combined refuge is planted on continuous corn, the MON 89034 x TC1507 x MON88017 x DAS-59122-7field may be planted on either continuous or rotated land (option encouraged where WCRW rotation resistant biotype may be present). Refuge options are based on the planting of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 in cotton or non-cotton growing regions and the insect pressure present in those locations. The refuge sizes for these regions are either 20% in cotton growing regions (i.e. 20 acres of non-Bt corn for every 80 acres MON 89034 x TC1507 x MON 88017 x DAS-59122-7 planted) or 5% in non-cotton growing regions (5 acres of non-Bt corn for every 95 acres of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 planted). If corn rootworms are significant within a region, the structured refuge must be planted as an in-field or adjacent refuge using corn hybrids that do not contain Bt technologies for the control of corn borers or corn rootworms. It can be planted as a block within or adjacent (e.g., across the road) to the MON 89034 x TC1507 x MON 88017 x DAS-59122-7, perimeter strips (i.e., strips around the field), or in-field strips. If perimeter or in-field strips are implemented, the strips must be at least 4 consecutive rows wide. The refuge can be protected from lepidopteran damage by use of non-Bt insecticides if the population of one or more target lepidopteran pests of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 in the refuge exceeds economic thresholds. In addition, the refuge can be protected from CRW damage by an appropriate seed treatment or soil insecticide; however, insecticides labeled for adult CRW control must be avoided in the refuge during the period of CRW adult emergence. If insecticides are applied to the refuge for control of CRW adults, the same treatment must also be applied in the same timeframe to MON 89034 x TC1507 x MON 88017 x DAS-59122-7. Economic thresholds will be determined using methods recommended by local or regional professionals (e.g., Extension Service agents, crop consultants). If corn rootworms are not significant within a region, the structured refuge may be planted as an in-field or adjacent refuge or as a separate block that is within *1/2* mile of the MON 89034 x TCl507 x MON 88017 x DAS-59122-7 field. The structured refuge must be planted with corn hybrids that do not contain Bt technologies for the control of corn borers or corn rootworms. Economic thresholds will be determined using methods recommended by local or regional professionals (e.g., Extension Service agents, crop consultants).

Region	Refuge size	In-field or adjacent refuge is allowed	Refuge separated by up to 1/2 mile is allowed
Cotton growing where CEW is a significant pest and WCRW, NCRW and MCRW are not significant: AR, NC, SC,GA, FL, TN (only the counties of Carroll, Chester, Crockett, Dyer, Fayette, Franklin, Gibson, Hardeman, Hardin, Haywood, Lake, Lauderdale, Lincoln,	20% non-Bt corn	Yes	Yes

Region	Refuge size	In-field or adjacent refuge is allowed	Refuge separated by up to 1/2 mile is allowed
Madison, Obion, Rutherford, Shelby, and Tipton) AL, MS, LA, VA (only the counties of Dinwiddie, Franklin City, Greensville, Isle of Wight, Northampton, Southampton, Suffolk City, Surrey, and Sussex)			
Cotton growing where CEW is a significant pest and WCRW, NCRW, and/or MCRW are significant: TX (except the counties of Carson, Dallam, Hansford, Hartley, Hutchinson, Lipscomb, Moore, Ochiltree, Roberts, and Sherman), OK (only the counties of Beckham, Caddo, Comanche, Custer, Greer, Harmon, Jackson, Kay, Kiowa, Tillman, and Washita), MO (only the counties of Dunkin, New Madrid, Pemiscot, Scott, and Stoddard).	20% non-Bt corn	Yes	No
Cotton growing where CEW is not a significant pest and WCRW, NCRW and MCRW are not significant: NM, AZ, CA, NV	5% non-Bt corn	Yes	Yes
Non-cotton growing where WCRW, NCRW and MCRW are not significant OR, WA, ID, MT, WY, UT, VA (except the counties of Dinwiddie, Franklin City, Greensville, Isle of Wight, Northampton, Southampton, Suffolk City, Surrey, and Sussex), WV, PA, MD, DE, CT, RI, NJ, NY, ME, MA, NH, VT, HI, AK, TN(except the counties of Carroll, Chester, Crockett, Dyer, Fayette, Franklin, Gibson, Hardeman, Hardin, Haywood, Lake, Lauderdale, Lincoln, Madison, Obion, Rutherford, Shelby, and Tipton)	5% non-Bt corn	Yes	Yes
Non-cotton growing where WCRW, NCRW and/or MCRW are significant: KS, NE, SD, ND, MN, IA, MO (except	5% non-Bt corn	Yes	No

Region	Refuge size	In-field or adjacent refuge is allowed	Refuge separated by up to 1/2 mile is allowed
the counties of Dunkin, New Madrid, Pemiscot, Scott, and Stoddard), IL, WI, MI, IN, OH, KY, CO, OK (except the counties of Beckham, Caddo, Comanche, Custer, Greer, Harmon, Jackson, Kay, Kiowa, Tillman, and Washita), TX (only the counties of Carson, Dallam, Hansford, Hartley, Hutchinson, Lipscomb, Moore, Ochiltree, Roberts, and Sherman)			

b) Grower Agreement for *MON 89034 x TC1507 x MON 88017 x DAS-59122-7* Corn

1) Persons purchasing MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn must sign a grower agreement. The term "grower agreement" refers to any grower purchase contract, license agreement, or similar legal document.

2) The grower agreement and/or specific stewardship documents referenced in the grower agreement must clearly set forth the terms of the current IRM program. By signing the grower agreement, a grower must be contractually bound to comply with the requirements of the IRM program.

3) Monsanto and Dow must implement a system (equivalent to what is already approved for previously registered Monsanto and Dow *Bt* corn products), which is reasonably likely to assure that persons purchasing *MON* 89034 x TC1507 x MON 88017 x DAS-59122-7 corn will affirm annually that they are contractually bound to comply with the requirements of the IRM program. A description of the system must be submitted to EPA within 90 days from the date of registration.

4) Monsanto and Dow must use a grower agreement and must submit to EPA, within 90 days from the date of registration, a copy of that agreement and any specific stewardship documents referenced in the grower agreement. If Monsanto and Dow wishe to change any part of the grower agreement or any specific stewardship documents referenced in the grower agreement that would affect either the content of the IRM program or the legal enforceability of the provisions of the agreement relating to the IRM program, 30 days prior to implementing a proposed change, Monsanto and Dow must submit to EPA the text of such changes to ensure that it is consistent with the terms and conditions of this registration.

5) Monsanto and Dow must implement a system (equivalent to what is already approved for previously registered Monsanto and Dow *Bt* corn products), which is reasonably likely to assure

that persons purchasing MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn sign grower agreement(s). A description of the system must be submitted to EPA within 90 days from the date of registration.

6) Monsanto and Dow shall maintain records of all MON 89034 x TC1507x MON 88017 x DAS-59122-7 corn grower agreements for a period of three years from December 31st of the year in which the agreement was signed.

7) Beginning on January 31, 2011 and annually thereafter, Monsanto and Dow shall provide EPA with a report on the number of units of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn seed shipped and not returned, and the number of such units that were sold to persons who have signed grower agreements. The report shall cover the time frame of a twelve-month period. Note: The first report shall contain the specified information from the time frame starting with the date of registration and extending through the 2010 growing season.

8) Monsanto and Dow must allow a review of the grower agreements and grower agreement records by EPA or by a State pesticide regulatory agency if the State agency can demonstrate that confidential business information, including names, personal information, and grower license number, will be protected.

c) IRM Education and IRM Compliance Monitoring Program for *MON 89034 x TC1507 x MON 88017 x DAS-59122-7*Corn

1) Monsanto and Dow must design and implement a comprehensive, ongoing IRM education program designed to convey to MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn users the importance of complying with the IRM program. The education program shall involve the use of multiple media, e.g. face-to-face meetings, mailing written materials, EPA-reviewed language on IRM requirements on the bag or bag tag, and electronic communications such as by internet, radio, or television commercials. Copies of the materials will be provided to EPA for their records. The program shall involve at least one written communication annually to each MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn user separate from the grower technical guide. The communication shall inform the user of the current IRM requirements. Monsanto and Dow shall coordinate its education program with the educational efforts of other registrants and other organizations, such as the National Corn Growers Association and state extension programs.

2) Annually, Monsanto/Dow shall revise, and expand as necessary, its education program to take into account the information collected through the compliance survey and from other sources. The changes shall address aspects of grower compliance that are not sufficiently high.

3) Beginning January 31, 2011, Monsanto and Dow must provide a report to EPA summarizing the activities it carried out under its education program for the prior year. Annually thereafter, Monsanto and Dow must provide EPA any substantive changes to its grower education activities

as part of the overall IRM compliance assurance program report. Monsanto/Dow must either submit a separate report or contribute to the report from the industry working group, Agricultural Biotechnology Stewardship Technical Committee (ABSTC).

4) Given that MON 89034 x TC1507 x MON 88017 x DAS-59122-7 will likely have different refuge strategies for lepidoptera and CRW than other registered Bt corn products, Monsanto/Dow must submit a revised compliance assurance program (CAP) within 90 days of the date of registration. This revised CAP must be found acceptable by BPPD by April 1, 2010. This strategy should be specific for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 and the new refuge requirements. Availability of non-Bt corn refuge seeds in desirable varieties must be addressed. Compliance is an area of ongoing concern -- recent data have shown that refuge compliance for Bt corn has fallen in recent years.

d) Insect Resistance Monitoring and Remedial Action Plans for *MON 89034 x TC1507 x MON 88017 x DAS-59122-7* Corn

Existing programs for resistance monitoring and remedial action that were established for MON 89034 (Cry1A.105 and Cry2Ab2), MON 88017 (Cry3Bb1), and Herculex Xtra (Cry1F and Cry34Ab1/35Ab1) should be applicable to MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn. In light of potentially lower overall structured Bt corn structured refuge, the CRW resistance monitoring program must be expanded (i.e. with additional sampling and collection sites or improved monitoring techniques). Also, a revised definition of "resistance" may be needed for the CRW monitoring and remedial action plans based on recent research and selection experiments (Lefko et al. 2008; Meihls et al. 2008). Monsanto/Dow must submit a revised resistance monitoring and remedial action plan within 90 days of the date of registration that must be found acceptable to BPPD by April 1, 2010.

A report on results of resistance monitoring and investigations of damage reports must be submitted to the Agency annually by August 31st each year, beginning in 2011, for the duration of the conditional registration.

e) Annual Reporting Requirements for *MON 89034 x TC1507 x MON 88017 x DAS-59122-7* Corn

1) Annual Sales: reported and summed by state (county level data available by request) January 31st each year, beginning in 2011;

2) Grower Agreements: number of units of MON 89034 x TC1507 x MON 88017 x DAS-59122-7corn seed shipped or sold and not returned, and the number of such units that were sold to persons who have signed grower agreements, January 31st each year, beginning in 2011;

3) Grower Education: substantive changes to education program completed previous year, January 31st each year, beginning in 2011;

4) Compliance Assurance Program: compliance assurance program activities and results for the prior year and plans for the compliance assurance program for the current year, January 31st each year, beginning in 2011;

5) Compliance Survey Results: results of annual surveys for the prior year and survey plans for the current year; full report January 31st each year, beginning in 2011;

6) Insect Resistance Monitoring Results: results of monitoring and investigations of damage reports, August 31st each year, beginning in 2011.

Additional Terms and Conditions as of November 22, 2011

1) The Agency recognizes that large corn rootworm populations, environmental conditions, and protein expression levels can influence corn root damage and may affect the definition of suspected CRW resistance. The Agency plans to work with the registrants to refine the definition of suspected resistance based on these factors. Until such time that the Agency accepts a modified definition of suspected resistance to corn rootworm, resistance will be suspected in cases where the average root damage in the SmartStax field is > 0.5 on the nodal injury scale (NIS) and the frequency of SmartStax with > 0.5 nodes destroyed exceeds 50% of the sampled plants.

2) Within 90 days of this amendment, you must submit an enhanced rootworm resistance monitoring plan for SmartStax that accounts for reports of suspected and/or confirmed resistance. The rootworm resistance monitoring plan and the revised definitions for suspected and confirmed resistance for SmartStax must be found acceptable to BPPD by May 1, 2012 and utilized by The registrant beginning in the 2012 season. This enhanced monitoring program should:

   o Be practical and adaptable, and provide information on relevant changes in corn rootworm population sensitivity to SmartStax;

   o Be focused on areas where the potential for resistance is greatest for SmartStax and for the corn rootworm active single event components of SmartStax (Cry3Bb1and Cry34Ab1/Cry35Ab1), based on available information on historical pest pressure, unexpected performance issues, historical suspected and/or confirmed resistance incidents as currently defined or as modified in EPA accepted enhanced monitoring programs, prevailing agronomic practices (e.g. crop rotation versus continuous corn), and academic and extension publications on Bt corn field performance;

- o Involve coordination to the extent possible with other stakeholders, such as academic and extension experts in the states where corn rootworm is a major pest, other registrants of SmartStax, and other registrants of similar products, as appropriate;

- o Be responsive to incidents of suspected or confirmed resistance to the registrant's other products containing the same active ingredient(s), as well as to publicly available reports of suspected or confirmed resistance to other *Bt* protein toxins in SmartStax.

3) Within 90 days of this amendment, you must submit an enhanced remedial action plan for SmartStax that includes actions to be taken in response to both suspected and confirmed resistance. This remedial action plan must include a description of steps to be taken in response to customer product performance inquiries and annual reporting to the agency on the outcomes of investigations into any such inquiries that might indicate potential resistance. The program must include revised definitions of unexpected damage to SmartStax corn that could indicate potential suspected resistance. The enhanced remedial action plan must be found acceptable to BPPD by May 1, 2012.

4) The Grower Guide or its supplements must include language directing the user to contact a company representative if they observe unexpected insect feeding damage to their SmartStax corn. As part of its follow up on reports of unexpected damage to SmartStax corn, the registrant must determine the nodal injury scale (NIS) of affected corn. If the NIS results fall within the definition of suspected resistance for SmartStax, then until such time as the Agency accepts a modified remedial action plan, the registrant must provide specific guidance to affected growers in managing corn rootworms in the affected fields. This will include 1) providing specific grower guidance to control the adult stage of corn rootworms, where adult beetles are still present and laying eggs during the season that unexpected damage meets the suspected resistance definition; and 2) where the grower continues to be an existing customer of the registrant or seed company licensee into the following season, providing specific grower guidance and assistance to use an additional or alternative pest control method during the season following the initial finding that unexpected damage meets the suspected resistance definition.

5) The registrant will submit additional modeling, scientific literature, and other scientific information addressing the impact of pyramid PIP use in areas of confirmed resistance to one of the rootworm-active components of the pyramid by August 30, 2012.

6) Should resistance to any of the constituent toxins of SmartStax be confirmed (from target pest populations collected in 2012 or prior growing seasons) in accordance with the existing definition of "confirmed resistance" for the appropriate toxin, EPA will reassess and, if EPA concludes it is necessary, The registrant will revise the refuge/seed blend requirements for SmartStax. The registrants may independently submit updated definitions of confirmed resistance for their respective SmartStax active proteins for EPA's consideration in order to harmonize and/or keep definitions current with scientific standards; any such submission must be found acceptable to BPPD by May 1, 2012. EPA will incorporate all relevant scientific information (including the data required above) in its reassessment of the refuge/seed blend requirements. The revised refuge/seed blend requirements will be effective for the following growing season (after resistance confirmation) in the geographic areas in which resistance was confirmed. The geographic area of confirmed resistance could be less than a single county, a single county, or multiple counties, depending on EPA's analysis of the collected data.

7) For the SmartStax block refuge products, submit a revised Compliance Assurance plan by February 28, 2012.

V. Contact Person at EPA

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DISCLAIMER: The information in this Pesticide Fact Sheet is a summary only and is not to be used to satisfy data requirements for pesticide registration. Contact the Senior Regulatory Specialist listed above for further information.

GLYPHOSATE

SUMMARY

Background

Glyphosate, commonly known by its original trade name Roundup™ (manufactured by Monsanto), is the world's most widely used herbicide. Glyphosate-based herbicides are manufactured by many companies in many countries.

Glyphosate is sprayed on numerous crops and plantations, including nearly 80% of genetically modified (GM) crops (canola, corn, cotton, soybean, sugar beet); with relatively high levels permitted as residues in food and animal feed. It is used as a pre-harvest desiccant, and because it is a systemic herbicide it cannot be completely removed from food by washing, peeling or processing. It is widely used in home gardens and public places including roadsides. Human exposure is widespread and constantly recurring.

Very aggressive public relations and marketing by its developer, Monsanto, has resulted in the widespread belief that glyphosate is 'safe'. Registration processes have generally supported this attitude, and there are no national or international bans. However, independent scientific studies and widespread poisonings in Latin America (resulting from aerial application) are beginning to reveal the true effects of glyphosate-based herbicides. Now France's Supreme Court has upheld judgements by two previous courts that "Monsanto falsely advertised its herbicide as 'biodegradable' and claimed it 'left the soil clean'" (Anon 2009).

Poisonings

Glyphosate herbicides have been frequently used in self-poisonings and many deaths have occurred, especially in Asia. There have also been many cases of unintentional poisonings amongst users and bystanders. Widespread poisonings have occurred in Latin America as a result of aerial spraying of GM soybean crops, and of coca crops in Colombia—effects being recorded as far as 10 km away from the supposed spray zone. The coca spraying (instigated by a US government funded program to eliminate cocaine production in Colombia) has also resulted in widespread animal deaths and food crop losses. Symptoms of poisoning commonly reported from unintentional exposure include vomiting, diarrhoea, abdominal pain, gastrointestinal infections, itchy or burning skin, skin rashes and infections (particularly prevalent in children), blisters, burning or weeping eyes, blurred vision, conjunctivitis, headaches, fever, rapid heartbeat, palpitations, raised blood pressure, dizziness, chest pains, numbness, insomnia, depression, debilitation, difficulty in breathing, respiratory infections, dry cough, sore throat, and unpleasant taste in the mouth. Other effects reported include balance disorder, reduced cognitive capacity, seizures, impaired vision, smell, hearing and taste, drop in blood pressure, twitches and tics, muscle paralysis, peripheral neuropathy, loss of gross and fine motor skills, excessive sweating, and severe fatigue.

Acute Toxicity

Glyphosate has a low toxicity rating (WHO Table 5) despite the substantial evidence of adverse health effects. Surfactants added to formulated glyphosate products may be more toxic: the surfactant POEA in Roundup is 2 to 3 times more toxic than the glyphosate itself. There are a number of other chemicals added to glyphosate formulations or contaminating them; some are known to be harmful, but many are regarded as trade secrets and it is unknown which might be contributing to the health effects.

Glyphosate

Long-term Toxicity

Recently scientists have found harmful effects on human cells at levels of glyphosate too low to have a herbicidal effect, some at levels similar to those found in food. These effects are amplified by the adjuvants in the Roundup formulation, which assist penetration of the cells by glyphosate. Several researchers have reported that glyphosate appears to accumulate in human cells.

Cancer, genotoxicity, endocrine disruption, reproduction

The International Programme on Chemical Safety (IPCS) and the United States Environmental Protection Agency (US EPA) have declared that glyphosate is not carcinogenic to humans. The US EPA originally classified glyphosate as a Group C "possible human carcinogen", then re-classified it as Group D "not classifiable as to human carcinogenicity", then as Group E "evidence of non-carcinogenicity in humans", and then in 2006 rephrased this as "Group E carcinogen with no evidence of human carcinogenicity".

Yet there is substantial laboratory and some epidemiological evidence that points to the opposite conclusion. Some researchers have concluded that glyphosate and its formulations clearly present a risk of carcinogenic, mutagenic, and reproductive effects on human cells.

Numerous laboratory studies have shown that glyphosate and the Roundup formulation can be genotoxic and endocrine disrupting. One study summarises these effects occurring at doses substantially lower than those used in agriculture, or permitted as residues: at 0.5 mg/kg (40 times lower than levels permitted in soybeans in the US) they were anti-androgenic; at 2 mg/kg they were anti-oestrogenic; at 1 mg/kg they disrupted the enzyme aromatase; at 5 mg/kg they damaged DNA, and at 10 mg/kg there were cytotoxic. These effects can result in crucial outcomes for sexual and other cell differentiation, bone metabolism, liver metabolism, reproduction, development and behaviour, and hormone dependent diseases such as breast and prostate cancer (Gasnier et al 2009).

Studies have demonstrated that glyphosate and/or Roundup cause genetic damage in human lymphocytes and liver cells; bovine lymphocytes; mouse bone marrow, liver, and kidney cells; fish gill cells and erythrocytes; caiman erythrocytes; tadpoles; sea urchin embryos; fruit flies; root-tip cells of onions; and in Salmonella bacteria. Other studies have shown that it causes oxidative stress, cell-cycle dysfunction, and disruption to RNA transcription, all of which can contribute to carcinogenicity.

Laboratory studies have shown that very low levels of glyphosate, Roundup, POEA, and the metabolite AMPA all kill human umbilical, embryonic and placental cells. Roundup can reduce sperm numbers, increase abnormal sperm, retard skeletal development, and cause deformities in amphibian embryos.

Exposure to glyphosate-based herbicides, even at very low doses may result in reproductive and hormonal problems, miscarriages, low birth weights, birth defects, and various cancers—especially haematological cancers such as non-Hodgkin's lymphoma, and hormonal cancers such as breast cancer.

Several epidemiological studies have linked exposure to glyphosate with non-Hodgkin's lymphoma, hairy cell leukaemia, multiple myeloma, DNA damage; and one study with spontaneous abortions and pre-term deliveries.

Neurological

Glyphosate is assumed by regulators to have no neurological effects—the US EPA did not require neurotoxicity studies to be carried out for the registration of Roundup. However there is emerging evidence that glyphosate can affect the nervous system, and in particular areas of the brain associated with Parkinson's disease. In one case study glyphosate exposure was linked to 'symmetrical parkinsonian syndrome'. An epidemiological study of children identified a link with Attention-Deficit/Hyperactivity Disorder (ADHD).

Other effects

Glyphosate damages liver cells and interferes with a number of enzymes important in metabolism.

Environmental Effects

The environmental effects of glyphosate of greatest concern are those that occur at a subtle level, and can result in significant disruption of aquatic and terrestrial eco-systems, including the agro-ecosystem.

Aquatic effects

Glyphosate is water soluble, and is increasingly found in the environment at levels that have caused significant effects on species that underpin the entire aquatic food chain. Glyphosate and/or Roundup can alter the composition of natural aquatic communities, potentially tipping the ecological balance and giving rise to harmful algal blooms. It can have profound impacts on microorganisms, plankton, algae and amphibia at low concentrations: one study showed a 70% reduction in tadpole species and a 40% increase in algae. Insects, crustaceans, molluscs, sea urchins, reptiles, tadpoles, and fish can all be affected, with vulnerability within each group varying dramatically between species. Effects include reproductive abnormalities, developmental abnormalities and malformations, DNA damage, immune effects, oxidative stress, modified enzyme activity, decreased capacity to cope with stress and maintain homeostasis, altered behaviour, and impaired olfaction that can threaten their survival. Amphibians are particularly vulnerable. Roundup is generally more toxic than glyphosate, especially to fish.

Terrestrial effects

Soil and plant health

As with the aquatic environment, it is the subtle effects causing disruption of the ecosystem that are of greatest concern, particularly effects on the agroecosystem. Glyphosate is toxic to some but not all soil microorganisms, altering microbial community dynamics in ways that are harmful to plants and to ecological balance. It increases microorganisms capable of metabolising the chemical. It can reduce some beneficial organisms such as saprophytic fungi that decompose dead plant material and are important for soil fertility. Numerous studies have shown that glyphosate stimulates the growth of a number of fungal pathogens that cause diseases in many crops. The upsurge in use of glyphosate in no-till agriculture has brought about a resurgence of some diseases. Glyphosate binds micronutrients in the soil and causes micronutrient deficiencies in plants that increase their susceptibility to disease, decrease their vigour, and produce micronutrient-deficient food crops. It can reduce the plant's production of lignin and phenolic compounds, which are also important for disease resistance. It can reduce nitrogen-fixation in legumes such as soybean.

Glyphosate can alter the nutritional composition of foods, for example the protein and fatty acid content of soybeans. It can cause iron deficiency in soybeans, which is a concern for human health as human iron deficiency is widespread.

Earthworms and beneficial insects

Glyphosate has adverse effects on some earthworms; and a number of beneficial insects useful in biological control, particularly predatory mites, carabid beetles, ladybugs, and green lacewings. It can also adversely effect other insects that play an important part in ecological balance such as springtails, wood louse, and field spiders.

Birds and other animals

Glyphosate use may result in significant population losses of a number of terrestrial species through habitat and food supply destruction. There have been reports of numerous deaths of livestock and domestic animals as a result of the aerial spraying of glyphosate in Colombia.

Environmental Fate

Soils

Glyphosate is relatively persistent in soil, with residues still found up to 3 years later in cold climates. It is less persistent in warmer climates, with a half-life between 4 and 180 days. It is bound onto soil particles, and this was once thought to mean that glyphosate is not biologically active within soil, nor will it leach to groundwater. However it is now known that it can easily become unbound again, be taken up by plants or leach out, indicating a greater risk of groundwater contamination. It can reduce nitrogen and phosphate fertility of soils.

Water

Glyphosate is soluble in water, and slowly dissipates from water into sediment or suspended particles. Although it does break down by photolysis and microbial degradation, it can be persistent for some time in the aquatic environment, with a half-life of up to nearly 5 months, and still be present in the sediment of a pond after 1 year.

Residues of glyphosate have been found in a wide range of drains, streams, rivers, and lakes, in many countries including Canada, China, France, Netherlands, Norway, USA, and the UK. Urban use on road and rail sides is contributing significantly to this contamination, with residues being found in sewage sludge and wastewater treatment plants. Contamination of 'vernal pools'—pools that are shallow and disappear in dry weather—are a concern for amphibia, for which these water sources are critical.

Glyphosate

Residues have also been found in groundwater in Canada, Denmark, the Netherlands, and USA. They have been detected in the marine environment off the Atlantic Coast of France; and in the rain in Belgium and Canada.

Resistance

Fourteen weeds in 14 countries have developed resistance to glyphosate. Most of this resistance has been caused by the repeated use of glyphosate in GM crops and no-till agriculture. Some has resulted from a gradual evolution of exposed weed species, and some from gene flow from GM crops to weed relatives. The latter has been observed with sugar beet in France, canola in Canada, creeping bentgrass in USA, and also with corn and soybean. Now even Monsanto is recommending the use of other herbicides in addition to glyphosate in Roundup-Ready crops (crops genetically modified to be tolerant of Roundup), to slow the onset of resistance in weeds.

Climate Change effects

A number of glyphosate's adverse effects can be expected to increase with climate change: higher temperatures enhance glyphosate's reduction of chlorophyll and carotenoids in freshwater green algae, increase toxicity to fish, and increase susceptibility to *Fusarium* head scab in cereals.

Alternatives

There are numerous design, mechanical and cultivational practices, as well as some non-chemical herbicides based on plant extracts, that can be used instead of glyphosate herbicides, depending on the weed species and the situation.

Chemical Profile

Common name

Glyphosate

Common trade name

Roundup

Chemical names and form

N-(phosphonomethyl)glycine

Glyphosate is a weak organic acid that consists of a glycine moiety (part of a molecule) and a phosphonomethyl moiety.

Technical grade glyphosate is a colourless, odourless crystalline powder, formulated as water-soluble concentrates and granules.

Most formulations contain the isopropylamine ammonium salt of glyphosate (glyphosate-isopropyl ammonium).

Molecular formula

$C_3H_8NO_5P$

Chemical group

Phosphinic acid

Other related chemicals

Glyphosate, diammonium salt
Glyphosate, dimethylammonium salt (glyphosate dimethylamine)
Glyphosate, ethanolamine salt
Glyphosate, monoammonium salt (glyphosate sel d'ammonium)
Glyphosate, potassium salt
Glyphosate, sesquisodium (or sodium) salt
Glyphosate, trimethylsulfonium salt (glyphosate-trimesium)

CAS numbers

Glyphosate	1071-83-6
Isopropylamine salt	38641-94-0
Monoamine salt	114370-14-8
Diammonium salt	69254-40-6
Sesquisodium salt	70393-85-0
Glyphosate-trimesium	81591-81-3
(Aminomethyl)phosphonic acid	1066-51-9

Trade names

Because glyphosate is so widely used and is off-patent, there are now very many generic formulations—Malaysia alone had 311 registered formulations containing glyphosate in February 2009—so there is a very large number of trade names.

In many cases glyphosate formulations can be identified by the word G360, G450, G510, or G580, preceded by a trader's name. The number indicates the concentration of glyphosate in the formulation, i.e. G360 has 360 g/l of glyphosate.

In some cases only the term 'Herbicide' is used, preceded by a variety of names such as Farmers Own, Growers, Harvest, etc.

Others make a play on the original product 'Roundup' by including 'up' in the name (Bright Up, Conto-Up, Dry-Up, Farm Up, Foldup, Ken-Up, Kleenup, Klin-Up, Move-Up, Set-Up, Sunup, Take-Up, Touch Up, Wes-Up, Zap Up); or the opposite, 'down' (Touchdown, Turndown); or 'round' (Myround, Roundsate, Seround).

Some names are variations of the word glyphosate (Glifosate, Glifosato, Glyfo, Glyfosaat, Glyfosat, Glymax, Glyphogan, Glyphosat, Glyphotis); use the last syllable of glyphosate (Ancosate, Envisate, Farmfosate, Gofosate, Herbisate, Ken-phosate, Masate, Megasate, Narscosate, Pilarsate, Sulfosate, Sulfosato, Supresate, Tecforsate, Vefosate); or use the chemical constituent glycine (Glyacid, Glycel, Glycin). Many more trade names are in local languages.

Many other trade names bear no distinguishable relationship to Roundup or glyphosate. Some of these attempt to present a benign image (Aglow, Ecomax, Esteem, Granny's Herbicide, Lotus, Spirit, S-Star, Vision); but many more do just the opposite (Ammo, Armada, Arrow, Assassin, Avenger, Challenge, Decimate, E-Kill, Fire, Frontier, Harass, Hatchet, Knockout, Monster, Mustang, Pounce, Punch, Q-Weapon, Raider, Rival, Rodeo, Salute, Samurai, Scud, Sentry, Shoot, Siren, Slash, Smash, Squadron, Stampede, Sting, Swing, Thunder, Tomahawk, Trounce, Turbo, Typhoon, Wallop). Others just try to indicate the product kills weeds (Weedact, Weedcut, Weed-go, Weed Hoe, Weedo, Weego).

Some formulations combine glyphosate with other herbicides such as aminopyralid (Broadnet), 2,4-D (Bimasta, Campaign, Evo, Hat-trick, Kontraktor, Landmaster), dicamba (Fallowmaster), diquat (A-13692B), imazapyr (Tackle, Imasate), MCPA (Fusta, Rapid, Rextor, Panton), metsulfuron-methyl (Fusion), picloram (Fusta), pyrithiobac sodium (Staple Plus, a pre-plant herbicide for glyphosate-resistant soybeans), simazine (Ricochet), terbuthylazine (Folar, Terminate), and triclopyr (Glytron). The formulation Tag G2, registered in New Zealand, contains glyphosate, amitrole, oxyfluorfen, and terbuthylazine.

Inerts and contaminants

Glyphosate formulations may contain a number of so-called 'inert' ingredients or adjuvants, most of which are not publicly known as in many countries the law does not require that they be revealed. Some information is available about formulations sold in the US, and the following list of 'inerts', provided by Cox (2004), can be expected to be found in products in many other countries. The list is not exhaustive.

POEA (polyoxyethylene alkylamine)
This is the most well known inert as it is contained in the original Roundup formulation. Registration data in New Zealand showed Roundup contained 18% POEA (Watts 1994).

- eye irritant, toxic to fish

Propylene glycol

- genetic damage, reduced fertility, and anaemia in laboratory tests

Glycerine

- genetic damage in human cells and laboratory animals
- reduced fertility in laboratory animals

Sodium sulfite

- genetic damage in human cells and laboratory animals

Sodium benzoate

- genetic damage in human cells and laboratory animals
- developmental problems and reduced newborn survival in laboratory animals

Sorbic acid

- severe skin irritant
- genetic damage in laboratory tests

Sodium salt of o-phenylphenol

- skin irritant
- genetic damage and cancer in laboratory animals

Light aromatic petroleum distillate

- reduced fertility, and growth of newborns, in laboratory animals

Methyl p-hydroxybenzoate

- genetic damage in laboratory animals

3-iodo-2-propynyl butyl carbamate

- thyroid damage and decreased growth in laboratory animals

5-chloro-2-methyl 3(2H)-isothiazolone

- genetic damage and allergic reactions in laboratory tests

Other constituents of surfactants recommended for use with Monsanto's Rodeo formulation include:

- polyol fatty acid esters
- polyoxyethyl polyol fatty acid esters
- paraffin base petroleum oil
- propionic acid
- alkylpolyoxyethylene ether
- octylphenoxypolyethoxyethanol – skin and eye irritant
- n-butanol
- compounded silicone
- nonylphenoxypolyethoxyethanol – also used as a spermicide
- silicone antifoam compound
- isopropanol
- polydimethylsiloxane

(Diamond & Durkin 1997)

Impurities found in technical grade glyphosate include *N*-nitroso-*N*-phosphonomethyl-glycine (also called *N*-Nitrosoglyphosate) (US EPA 1993). *N*-nitroso compounds are "genotoxic, carcinogenic to animals, and may play a role in human cancer development" (Hebels et al 2009).

Registration data for Roundup in New Zealand showed the presence of 1% sulphuric acid and trace amounts of phosphoric acid (Watts 1994).

POEA is contaminated with 1,4-dioxane, reported at levels of 0.03% by the US EPA in 1991. This substance causes liver and nasal cancer in laboratory rodents (NTP 2005; Kano et al 2009) and is "reasonably anticipated to be a human carcinogen" (NTP 2005).

It is clear, then, that exposure to a glyphosate-based herbicide entails exposure to a wide range of other chemicals as well as the glyphosate, about which little information is available and the full health effects of which have not been established. Some, such as POEA, are known to be more acutely toxic than the glyphosate itself. Others are clearly capable of causing serious chronic effects.

Metabolites

The main metabolite of glyphosate is (aminomethyl) phosphonic acid (AMPA).

N-acetyl-glyphosate (also called *N*-acetyl-*N*-(phosphonomethyl)glycine) is a metabolite formed when glyphosate is applied to genetically modified 'Optimum Gat' soybean (FR 2008). It is assumed by the US EPA (2006) to be "toxicologically equivalent to glyphosate".

N-acetyl-glyphosate is in turn metabolised to *N*-acetyl (aminomethyl)phosphonic acid (*N*-acetyl-AMPA)—which is considered by the US EPA to be of low toxicity and "of limited concern" (FR 2008).

Mode of action in weeds

The commonly accepted explanation of glyphosate's mode of action is as follows: glyphosate inhibits the enzyme 5-enolpyruvyl-shikimate 3-phosphate synthase, which is essential for the formation of aromatic amino acids (phenylalanine, tyrosine, tryptophan) in plants, by what is commonly referred to as the shikimic pathway. Without amino acids the plants cannot make protein; growth ceases, followed by cellular disruption and death. The shikimic pathway is not found in the animal kingdom, hence glyphosate was thought to be "relatively non-toxic to mammals" (Anadón 2009).

However, there may be more to it than that: after glyphosate is absorbed through the foliage, it is translocated within the plant, down to the roots and released into the rhizosphere (soil surrounding the roots) (Kremer & Means 2009), where it disrupts the soil and root microbial community. As much as 80% of glyphosate absorbed after foliar application is translocated to the shoot apex and root tips (Cakmak et al 2009). Glyphosate's herbicidal action is now suggested to be in part due to, on the one hand stimulation of soil-born pathogens which colonise the roots of the plants, and on the other hand the reliance of many plant defences on the shikimic acid pathway—so that the combination of increased pathogens and increased susceptibility to them is an important element in the death of the plant (Johal & Huber 2009). As far back as 1984 Johal & Rahe demonstrated that the death of bean plants treated with glyphosate resulted from parasitisation by fungal root rot pathogens in the growth medium (refer to section on Plant diseases for more on this).

Uses

Glyphosate is believed to be the world's most heavily used pesticide (Duke & Powles 2008b), with over 600 thousand tonnes used annually (CCM International 2009b).

It is a broad spectrum (non-selective), systemic, post-emergence herbicide used to control annual and perennial plants including grasses, sedges, broadleaf weeds and woody plants. It is used for crops, orchards, glasshouses, plantations, vineyards, pastures, lawns, parks, golf courses, forestry, roadsides, railway tracks, industrial areas, and home gardening.

It is used for pre-harvest desiccation of cotton, cereals, peas, beans, and other crops; for root sucker control; and for weed control in aquatic areas.

The sodium salt (Quotamaster) is used as a growth regulator on sugar cane—to hasten ripening, enhance sugar content, and promote earlier harvesting—and on peanuts.

Glyphosate is also used to destroy drug crops grown in Colombia. Since 2000, the USA has been funding the Colombian government to aerial spray crops of coca and opium—in 2006 alone 171,613 hectares were sprayed. The area sprayed has increased every year since 2000, with a 24% increase from 2005 to 2006 (Leahy 2007). The product used is Roundup-Ultra containing 43.9% glyphosate, POEA, and another adjuvant, Cosmo-Flux 411 F.

Weak solutions of the Roundup formulation are used to devitalise some plant material before importation into Australia and New Zealand to reduce biosecurity risks by preventing propagation of the plant material. For example, the New Zealand biosecurity authority requires that the stems of cut flowers and foliage are immersed to within 50 mm of the flower in a 0.5% solution of Roundup for 20 minutes—this reputedly prevents propagation but allows about a week of shelf life (MAF 2002).

Glyphosate is patented as a synergist for mycoherbicides (natural fungi used for biological control of weeds), as it enhances the virulence of the fungi (Johal & Huber 2009).

Glyphosate

Glyphosate is applied by a wide-range of methods, including backpack sprayers, aerial spraying, ground broadcast sprayers of various types, shielded and hooded sprayers, wiper applications, sponge bars, injection systems, and controlled droplet applicators.

The main drivers for global glyphosate use in recent years have been no-till farming, biofuels production and, especially, the development of plants genetically modified to be tolerant of glyphosate (CCM International 2009a). The growing of GM corn, cotton, and soybean in the USA is credited with the eight-fold increase in glyphosate use between 1995 and 2005 (Johnson et al 2009).

Genetically modified (GM) crops

The first glyphosate-tolerant crop was soybean, introduced in the United States in 1996 (Dill et al 2008).

Now, over 80% of the current GM crop acreage worldwide is planted in 4 herbicide-tolerant crops, the vast majority of which are tolerant to high levels of glyphosate (a small amount are tolerant to glufosinate ammonium). The crops are soybean, maize, canola, and cotton, grown mainly in USA, Canada, Argentina, Brazil, and Paraguay (Villar & Freese 2008). By 2008 glyphosate-tolerant soybean was grown on 65.8 million ha (53% of global GM crops), maize on 37.3 million ha (30% of global GM), and cotton on 15.5 million ha (12% of global GM) (Yamada et al 2009).

About 95% of Argentina's annual crop of 47 million tonnes of soybean is the GM Roundup Ready soybean; 200 million litres of glyphosate are applied to it every year, mainly by aerial spraying. This monocultural soybean is grown on 42 million acres, accounting for nearly 50% of all farmland in Argentina (Trigona 2009; Valente 2009).

Bolivia also grows soybean; and Australia grows glyphosate-tolerant cotton and canola (ISAAA 2008). By 2007 about 75% of Australia's cotton was glyphosate-tolerant (Werth et al 2008).

In 2008, glyphosate-tolerant sugar beet was introduced in Canada and USA (James 2008).

On 24 June 2009, the U.S. Court of Appeals "reaffirmed its previous decision to uphold a ban on Roundup Ready (RR) alfalfa, because it could cause irreversible harm to organic and conventional crops, damage to the environment, and economic harm to farmers" (CFS 2009). About 100,000 ha of the GM alfalfa was grown in the USA in 2007 (James 2007).

Glyphosate-tolerant wheat and glyphosate-tolerant creeping bentgrass (turf grass for golf courses) have also been developed by Monsanto, but have not been commercialised.

Pioneer Hi-Bred International, a subsidiary of DuPont, has been developing glyphosate-tolerant corn and soybean containing the trait called 'Optimum Gat'. It proposes that the DuPont herbicide Staple Plus (containing glyphosate and pyrithiobac sodium) be used as a pre-plant herbicide, 10 months before planting (US EPA 2008). It also planned to introduce the trait into cotton and other crops (Pioneer 2007). Introduction of the corn is scheduled for 2010 and the soybean for 2011, once regulatory approval has been achieved (Gullickson 2009). However there appears to be some problems with the trait, and Monsanto is now suing DuPont (Monsanto 2009).

Manufacturers

The original manufacturer of glyphosate herbicides was the Monsanto Company of St Louis, Missouri, USA. It still manufactures them under various trade names including the original Roundup. However since the patent on Roundup expired, many other companies in many countries now also manufacture glyphosate-based herbicides. China is the largest producer, with its production capacity accounting for more than 40% of the global total (CCM International 2009b).

Regulatory Status

Glyphosate was first registered in the USA in 1974; it is now registered worldwide and is the most commonly used herbicide, especially on GM crops.

Very little regulatory action has been taken against glyphosate. In May 2009, the Environmental Lawyers Association of Argentina filed a lawsuit in Argentina's Supreme Court for a ban on glyphosate, citing the study by Professor Carrasco's team (reported in the section on Reproductive toxicology). Argentina's defence ministry has banned the planting of glyphosate-tolerant soybean on lands it rents to farmers. Early in 2009 a court order banned crop spraying of soybean fields near Ituzaingó Anexo suburb of the central Argentinean city of Córdoba after multiple health complaints. The ban now applies to all fields within 1,000 metres of residential areas in the province of Córdoba (Misculin 2009; Trigona 2009).

International regulatory action

None taken to date.

Toxicological Assessment

The toxicity database for glyphosate is considered by the US EPA (2006) to be "complete and without data gaps". However the US EPA did not require developmental neurotoxicity studies; neither did it require studies of its impact on hormones, or studies of inhalation toxicity.

Most of the studies used for registering glyphosate-based herbicides have been carried out on laboratory animals, often using high levels of exposure to demonstrate visible effect. More recent advances in testing using cell cultures have enabled toxicity of low levels of glyphosate to be determined with much higher sensitivity, eliciting the subtle effects that can be of profound importance to the organism. However, the results of these latter studies have generally not been used for registering the herbicides, and therefore registration outcomes do not reflect the potential and actual effects of glyphosate. Both types of studies are reported here.

Absorption and distribution

About 30-36% of glyphosate is absorbed through the gastrointestinal tract in laboratory animals, with 97.5% excreted unchanged in the faeces and urine together with small amounts of the metabolite AMPA. Less than 1% of the absorbed dose remains in the carcass, and this is primarily in the bone according to the US EPA (2006).

Absorption through the skin is said to be "low" (US EPA 1993), less than 3% (EC 2002).

Small amounts of glyphosate can be absorbed through the skin from contaminated clothing: one study showed that absorption from cotton fabric was 0.74%, half of that absorbed from an aqueous solution (1.42%) in the same study (Webster et al 1996).

Glyphosate is poorly metabolised in animals (<0.5%), to AMPA, according to the US EPA (1993). More recently, Anadón et al (2009) found 6.49% metabolism.

Poor absorption and rapid elimination of glyphosate are the reasons usually given for the assumption that normal exposure (i.e. not intentional self-poisoning) to glyphosate is unlikely to result in systemic effects (e.g. Williams et al 2000, an often-cited review).

However, recent independent work has shown that both glyphosate and AMPA were eliminated slowly from plasma and, although bioavailability was only 23.21%, it is likely that glyphosate is distributed throughout the body by the blood's circulation and there may be considerable diffusion of it into tissues to exert systemic effects (Anadón et al 2009).

Although Williams et al (2000) state that glyphosate does not bioaccumulate, recent findings by Professor Carrasco of Argentina indicate that glyphosate might be accumulating in cells (Valente 2009; Trigona 2009; Ho 2009).

Acute toxicity

The International Programme on Chemical Safety (IPCS) regards glyphosate as having very low acute toxicity to laboratory animals (IPCS 1994). However the commonly used surfactant, POEA, is at least four times more toxic than glyphosate.

US EPA (2006) toxicity categories for glyphosate:

- oral = category IV
- inhalation = category: none
- dermal = category IV
- eye irritation = category III
- skin irritation = category IV

The World Health Organisation Recommended Classification by Acute Hazard for glyphosate (WHO 2005):

- Class 5.

Lethal doses

The lethal dose, LD_{50}, is the dose that kills 50% of test animals.

1. <u>Glyphosate</u>

- Oral LD_{50} rat = >5,000 mg/kg
- Dermal LD_{50} rabbit = >5,000 mg/kg
- (US EPA 1993; IPCS 1994)
- Inhalation LC_{50} rat = >5 mg/l (EC 2002)

2. <u>Roundup</u>

- Oral LD_{50} rat = >5,000 mg/kg
- Dermal LD_{50} = >5,000 mg/kg
- Inhalation LC_{50} rat = 3.18 mg/kg

(Williams et al 2000)