FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

Supporting Document 2

ASSESSMENT OF GLYPHOSATE RESIDUES

SUMMARY AND CONCLUSIONS

Two novel residues are generated in maize 98140 plants following glyphosate application, namely N-acetyl glyphosate (NAG) and N-acetyl aminomethylphosphonic acid (N-acetyl AMPA). These residues are also generated in soy 356043 plants following application of glyphosate (Application 1006). A toxicological assessment of these compounds was conducted as part of the assessment of Application 1006 (link to FSANZ assessment: http://www.foodstandards.gov.au/standardsdevelopment/applications/applicationa1006food3900.cfm).

NAG and N-acetyl AMPA were concluded to be less toxic than glyphosate, which itself has low toxicity potential. On this basis, the establishment of a separate ADI for NAG and N-acetyl AMPA, was considered unnecessary. Therefore the current Australian ADI for glyphosate of 0.3 mg/kg bw/day remains appropriate for dietary risk assessment purposes.

NAG is the predominant residue detected in commodities derived from maize 98140 plants that have been treated with glyphosate. Parent glyphosate, AMPA, and N-acetyl AMPA are also detectable. Given that glyphosate is the only toxicologically-significant residue present on/in grain derived from maize 98140 plants, its measurement in material derived from maize 98140 plants is considered adequate for safety assessment purposes.

BACKGROUND

As part of its pre-market safety assessment of foods, which are derived from crops that are genetically modified (GM) for pesticide tolerance, FSANZ considers the generation of new residues or increased concentrations of known residues in the crop, following application of the pesticide. If new residues are generated that have not previously been assessed for safety then their toxicity must be considered as it may have implications for the determination of dietary risk or the residue definition of the maximum residue limit (MRL)[1]. The purpose of the MRL is to ensure the legitimate and safe use of pesticides on commodities grown in, or imported into, Australia or New Zealand.

The toxicology of glyphosate has been evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) on a number of occasions, most recently in 2004 (WHO 2004). In addition, the toxicology of AMPA was evaluated by the JMPR in 1997, when it was concluded to be of no greater toxicological concern than glyphosate (WHO 1997).

The ADI for humans is the level of intake of a chemical that can be ingested daily over an entire lifetime without appreciable risk to health. In Australia, ADIs for pesticides and veterinary medicines are established by the Office of Chemical Safety within the Department of Health and Ageing.

[1] The MRL is the maximum concentration of a residue, resulting from the registered use of an agricultural or veterinary chemical legally permitted or recognised as acceptable in or on a food, agricultural commodity, or animal feed.

The current ADI for glyphosate of 0.3 mg/kg bw/day was set in 1985[2] based on the no observed effect level (NOEL) of 30 mg/kg bw/day, the highest dose tested in a 2-year rat study, and using a 100-fold safety factor (10-fold intra and interspecies safety factors). There is currently no ADI for NAG, AMPA or N-acetyl AMPA.
In Australia, the Australian Pesticides and Veterinary Medicines Authority (APVMA) establish MRLs for pesticides. The APVMA has published a number of principles and options that may assist in the establishment of MRLs[3]. In particular, the inclusion of specific metabolites or degradation products in the residue definition depends on their toxicity. There is an existing glyphosate MRL for cereal grains in Standard 1.4.2 of the Code and the applicant has provided information to indicate that this MRL is appropriate for maize 98140. The residue definition is the *sum of glyphosate and aminomethylphosphonic acid (AMPA) metabolite, expressed as glyphosate*.

In New Zealand, MRLs are established by the Agricultural Compounds and Veterinary Medicines Group (ACVMG) within the NZ Food Safety Authority (NZFSA). There is no glyphosate MRL for maize currently listed in the NZ MRL Standard; however, there is a provision for residues of up to 0.1 mg/kg for agricultural compound/food combinations not specifically listed. In addition, the NZ MRL Standard recognises Codex standards for imported food. The Codex MRL for glyphosate in maize is 5 mg/kg (the residue definition only includes parent glyphosate).

As there is no application under consideration to grow maize 98140 in Australia, food derived from maize 98140 would most likely be imported from the US. The US Environment Protection Agency has amended the residue definition to include NAG and N-acetyl AMPA in the residue definition for glyphosate for soy but has not at this time changed it for maize.

NAG and N-acetyl AMPA are novel residues that have not previously been detected in conventional crops or currently approved GM glyphosate-tolerant maize (or other) plants containing the *cp4 epsps* gene. Maize 98140 plants also carry a second genetic modification conferring tolerance to acetolactate synthase (ALS)-inhibiting herbicides. Therefore, maize 98140 would also need to comply with existing Australian and New Zealand MRLs for ALS-inhibiting herbicides.

Residue studies

The applicant submitted residue chemistry studies that analysed the types and concentrations of residues generated in grain and processed fractions from maize 98140 following application of glyphosate (Daussin *et al.* 2008; Green 2007; Thiel 2007a; Thiel 2007b). All studies were conducted according to the principles of Good Laboratory Practice (GLP). There were some minor deviations from GLP; however, these deviations are not expected to affect the validity of the studies.

Residue trials were conducted at a number of sites in the USA and Canada to determine the levels of glyphosate and its metabolites in maize 98140 plants after a total seasonal glyphosate application following the label application rate. One pre-emergent and three foliar applications were made. The predominant (mean of 60%) residue in maize grain was NAG followed by parent glyphosate (mean of 16%), N-acetyl AMPA and AMPA. Mean levels of parent glyphosate and AMPA were 0.018 mg/kg and 0.011 mg/kg, respectively.

[2] http://health.gov.au/internet/main/publishing.nsf/Content/E8F4D2F95D616584CA2573D700770C2A/$File/ADI%20Report%20-%20Dec%202008.pdf
[3] http://www.apvma.gov.au/guidelines/rgl6.shtml

In a separate study in which maize 98140 was treated at 5-times the label application rate, there were no detectable residues of glyphosate, N-acetyl glyphosate, AMPA, or N-acetyl AMPA found in refined maize oil or starch derived from the grain of treated maize 98140.

DISCUSSION

Residue definition

The residue definition for a pesticide (for compliance with MRLs) is *that combination of the pesticide and its metabolites, derivatives and related compounds to which the MRL applies* (FAO 2002). With regard to GM crops, the principles for determining the residue definition are no different to those used for conventional crops; the residue definition should include toxicologically-significant compounds and those most suitable for monitoring compliance with Good Agricultural Practice (FAO 2002; OECD 2006). The residue definition is established on a case-by-case basis and takes into consideration a number of factors including the:

- toxicity of the metabolites, derivatives and related compounds compared to the parent compound;
- results of supervised trials;
- residue composition and levels in animal and plant metabolism studies; and
- analytical methods used to measure the residues (OECD 2006).

Results from residue trials submitted as part of the current application indicated that the predominant residue in maize grain was NAG followed by parent glyphosate, N-acetyl AMPA and AMPA. From a risk assessment perspective, the relatively higher levels of NAG generated in edible material derived from maize 98140 plants following application of glyphosate is not considered to pose any safety concerns because this compound is much less toxic than parent glyphosate. While N-acetyl AMPA is also detectable in GM plant material, it is present at much lower concentrations than NAG (or glyphosate) and similarly has limited toxicity potential. As neither NAG nor N-acetyl AMPA are toxicologically-significant compounds, it is unnecessary to include them in the residue definition for glyphosate for dietary risk assessment purposes.

There is no approval or any application under consideration to grow maize 98140 plants in Australia or New Zealand. Therefore, food commodities derived from maize 98140 plants would be imported into Australia and New Zealand, most likely from the USA. From a practical perspective, the MRL for glyphosate in the Code would be applicable to this imported material. Given that glyphosate is the only toxicologically-significant compound of the four residues considered as part of the current assessment, and that it is detectable in commodities derived from treated maize 98140 plants (albeit at relatively low levels), its measurement in imported material is considered adequate for safety assessment purposes. On this basis, the current residue definition for glyphosate, which appears in Standard 1.4.2 and is the sum of glyphosate and AMPA expressed as glyphosate, remains appropriate for safety assessment purposes.

CONCLUSIONS

- There are no safety concerns with regard to NAG and N-acetyl AMPA, which are less toxic than glyphosate.

- The establishment of a new or amended ADI for glyphosate and its residues, or a separate ADI for NAG and N-acetyl AMPA, is unnecessary.

- For GM maize imported into Australia, the current Australian residue definition for glyphosate remains appropriate for safety assessment purposes.

- For GM maize imported into New Zealand, consideration of whether the current residue definition is appropriate is the responsibility of the NFZSA.

REFERENCES

Daussin S, Nathan EC, Brown AM, and Gaddamidi V (2008) Optimum® GAT® – a new mode of glyphosate tolerance in plants. OECD Dossier for the assessment of glyphosate MRL's for the import of Optimum® GAT® maize grain and soybean seed. DuPont document number: DuPont-24731 AU. Unpublished report.

FAO (2002) Submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed (Available online at http://www.fao.org/ag/agp/agpp/pesticid/JMPR/Download/FAOM2002.pdf)

Green MA (2007) The metabolism of [^{14}C]glyphosate in Optimum™ GAT™ (Event DP-Ø9814Ø-6) field corn. DuPont Study number: DuPont-19529. Charles River Laboratories Project Number: 807194. Pioneer Study Number: PHI-2006-131. Unpublished report.

OECD (2006) Guidance document on the definition of residue. ENV/JM/MONO(2006)31. Series on Testing and Assessment Number 63, Series on Pesticides Number 31.

Thiel A (2007a) Magnitude of residues of glyphosate and degradates in aspirated grain and processed fractions (starch, grits, flour, refined oil (wet milling) refined oil (dry milling) and meal (dry milling) of a field corn line containing event DP-Ø9814Ø-6 following applications of glyphosate containing herbicides – United States and Canadian locations, Season 2006. DuPont Study Number: DuPont-19836. PHI Study Number: PHI-2006-187. ABC Study Number: 50165-1. Unpublished report.

Thiel A (2007b) Magnitude and decline of glyphosate and its degradates in/on green plant, forage, stover and grain of a corn line containing event DP-Ø9814Ø-6 GAT and ZM-HRA genes following a variety of tank mix applications of two glyphosate and rimsulfuron, tribenuron methyl, chlorimuron ethyl, and metsulfuron methyl containing herbicides at maximum label rates – United States and Canadian locations, Season 2006. DuPont Study Number: DuPont-20122. Pioneer Study Number: PHI-2006-045. ABC Study Number: 50165. Unpublished report.

WHO (1997) Toxicological and environmental evaluations 1994. Joint meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

WHO (2006) Pesticide residues in food – 2004 Joint FAO/WHO Meeting on Pesticide Residues. Part II—Toxicological. WHO/PCS/06.1, 2006