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An assessment of dietary exposure to glyphosate using refined deterministic and probabilistic methods

C.L. Stephenson [a, *], C.A. Harris [a]

[a] Exponent International Ltd, Hornbeam Park, Harrogate, HG2 8RE, UK

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ABSTRACT

Glyphosate is a herbicide used to control broad-leaved weeds. Some uses of glyphosate in crop production can lead to residues of the active substance and related metabolites in food. This paper uses data on residue levels, processing information and consumption patterns, to assess theoretical lifetime dietary exposure to glyphosate.

Initial estimates were made assuming exposure to the highest permitted residue levels in foods. These intakes were then refined using median residue levels from trials, processing information, and monitoring data to achieve a more realistic estimate of exposure. Estimates were made using deterministic and probabilistic methods. Exposures were compared to the acceptable daily intake (ADI)—the amount of a substance that can be consumed daily without an appreciable health risk.

Refined deterministic intakes for all consumers were at or below 2.1% of the ADI. Variations were due to cultural differences in consumption patterns and the level of aggregation of the dietary information in calculation models, which allows refinements for processing. Probabilistic exposure estimates ranged from 0.03% to 0.90% of the ADI, depending on whether optimistic or pessimistic assumptions were made in the calculations. Additional refinements would be possible if further data on processing and from residues monitoring programmes were available.

1. Introduction

Glyphosate[1] is a non-selective, systemic herbicide used for the control of annual and perennial grasses and broad-leaved weeds in agriculture, horticulture, plantation crops, orchards, vineyards, and forestry. It also has a variety of amenity and non-food crop uses, including aquatic weed control and weed control in non-cultivated areas (EFSA, 2013). Glyphosate acts by inhibiting 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), preventing the production of essential amino acids, which are required for protein synthesis. Conventional crops can be susceptible to the herbicidal action of glyphosate, and therefore, glyphosate is applied to soil at pre-planting or pre-emergence of arable or vegetable crops, and directly to weeds around the base of orchard trees and

Abbreviations: ADI, acceptable daily intake; AMPA, aminomethyl-phosphonic acid; BfR, Federal Institute for Risk Assessment; CF, conversion factor; CFR, Code of Federal Regulations; cPAD, chronic population-adjusted dose; CRD, Chemicals Regulation Directorate; CXL, Codex maximum residue limit; DAR, draft assessment report; DNFCS, Dutch National Food Consumption Survey; DEEM, Dietary Exposure Evaluation Model; EC, European Commission; EFSA, European Food Safety Authority; EPA, Environmental Protection Agency; EPSPS, 5-enolpyruvylshikimate-3-phosphate synthase; EU, European Union; FAO, Food and Agriculture Organization of the United Nations; FP7, 7th Framework Programme for Research and Technological Development; GAP, good agricultural practice; GAT, glyphosate-N-acetyltransferase; GEMS, Global Environment Monitoring System; GOX, glyphosate oxidoreductase; IEDI, international estimated daily intake; IUPAC, International Union of Pure and Applied Chemistry; JMPR, Joint FAO/WHO Meeting on Pesticide Residues; LOQ, limit of quantification; LOR, limit of reporting; MCRA, Monte Carlo Risk Assessment; MRL, maximum residue level; MS, member state; NAFTA, North American Free Trade Agreement; NDNS, National Diet and Nutrition Survey; NEDI, national estimated daily intake; NOAEL, no observed adverse effect level; NVS, National Nutrition Survey; OECD, Organization for Economic Cooperation and Development; PF, processing factor; PPR, Plant Protection Products and their Residues; PRiF, Expert Committee on Pesticide Residues in Food; PRIMo, Pesticide Residue Intake Model; RAC, raw agricultural commodity; RAR, renewal assessment report; RIVM, National Institute for Public Health and the Environment; STMR, supervised trials median residue; TMDI, theoretical maximum daily intake; UK, United Kingdom; US, United States of America; VELS, food consumption survey to determine food intake by infants and small children; WHO, World Health Organization.

* Corresponding author.
E-mail address: cstephenson@exponent.com (C.L. Stephenson).

[1] N-(phosphonomethyl)glycine (IUPAC; International Union of Pure and Applied Chemistry).

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vineyards. Limited uptake of glyphosate residues from the soil generally leads to low or non-detectable residues in the treated crops.

Pre-harvest applications of glyphosate can also be made to cereals, pulses, and oilseeds. These applications are used to control perennial and annual weeds in transgenic plant varieties, which are tolerant to glyphosate, or for the desiccation of non-tolerant crops prior to harvest. Transgenic varieties typically overproduce the EPSPS enzyme or contain microbial variants of the enzyme that are not inhibited by glyphosate. Other modifications include introduction of the glyphosate oxidoreductase (GOX) gene, which acts to convert glyphosate to a non-phytotoxic compound, aminomethylphosphonic acid (AMPA). In Europe, until 2009, the residue definition for the risk assessment of glyphosate in plants, based on the behaviour of glyphosate in these tolerant crops, included both glyphosate and AMPA.

The introduction of a glyphosate-N-acetyltransferase (GAT) gene, which detoxifies glyphosate by conversion to N-acetyl-glyphosate, then led to the extension of the residue definition to include N-acetyl-glyphosate and N-acetyl AMPA (EFSA, 2009b). The Joint Meeting on Pesticide Residues (JMPR) also applies a definition that includes N-acetyl-glyphosate and N-acetyl-AMPA when conducting assessments, whilst acknowledging that the N-acetyl metabolites are only relevant for crops containing the GAT gene. This residue definition also applies to the risk assessment of edible products of animal origin. Despite the inclusion of N-acetyl-glyphosate and N-acetyl-AMPA in the both the European Union (EU) and JMPR residue definitions for risk assessment, there are currently no commercial crops containing the GAT gene. Taking account of these residues in the risk assessment, based on their potential occurrence as measured in model residues trials, therefore over-estimates the actual exposure to glyphosate residues. The residue for monitoring and setting maximum residue levels (MRLs) purposes is defined as glyphosate for all plant and animal commodities (EC, 2013). The recent European Food Safety Authority (EFSA) conclusion on the peer review of glyphosate, following the evaluation for renewal of approval under Regulation (EC) No 1107/2009, recommends that N-acetyl-glyphosate also be included in the monitoring definition for sweet corn, oilseed rape, soya beans, maize, and animal commodities (EFSA, 2015b), although this is not currently the legal definition.

In 2004, a study by Harris and Gaston considered the chronic dietary exposure to glyphosate following the European Union review leading to Annex 1 inclusion in Council Directive 91/414/EEC (now approved under Regulation [EC] No 1107/2009). The study used the existing method for estimating chronic exposure and made stepwise refinement assumptions using the available processing information, pesticide residues monitoring data, and consumption data from the United Kingdom (UK) adult and toddler surveys for cereal products. The analysis focussed on the chronic exposure to treated cereals, and the refinements led to intakes accounting for 0.6% of the acceptable daily intake (ADI) of 0.3 mg/kg bw/day (EC, 2001), compared to 11% of the ADI using unrefined methods. Since this assessment was made, the maximum residue level (MRL) regulation (EC No 396/2005) has been introduced, which results in an MRL for every foodstuff listed in the associated Annex 1 commodity list (EC, 2014a), for any given pesticide. Where there are no intended uses of a particular pesticide, a default MRL applies, set at an analytically achievable level (currently 0.1 mg/kg in the case of glyphosate) (EC, 2013). A small number of additional MRL values have also been set on the basis of new uses within the European Union and for glyphosate-treated produce that may be imported into Europe. Furthermore, following the evaluation for renewal of approval under Regulation (EC) No 1107/2009, the EFSA has recommended that the ADI be revised to 0.5 mg/kg bw/day (EFSA, 2015b).

In 2013, the United States Environmental Protection Agency (US EPA) published a regulation establishing additional tolerances for glyphosate residues in or on multiple commodities within the fruits, root and tuber, and oilseeds crop groups (40 CFR Part 180.364) [EPA–HQ–OPP–2012–0132; FRL–9384–3] (EPA, 2013). In order to amend the tolerances, the EPA made an assessment of the safety of glyphosate based on the proposed and existing tolerances. The EPA concluded that dietary exposure to glyphosate does not result in acute effects and does not pose a cancer risk to humans. A chronic dietary exposure assessment was conducted assuming that 100% of crops consumed were treated and contained residues at the tolerance level. Intakes of glyphosate via food and water for the most exposed population, 1- to 2-year-old children, accounted for 13% of the chronic endpoint (chronic population adjusted dose [cPAD] of 1.75 mg/kg bw/day; EPA, 2006). The EPA therefore concluded with reasonable certainty that no harm will result to the general population or to infants and children in the United States from aggregate exposure, including intermediate residential exposure, to glyphosate residues.

In contrast to the more recent EPA dietary exposure assessment, the overall exposure for consumers in the EU has not been comprehensively re-examined at the EU level or by EFSA since 2004. Subsequently, new EU uses of glyphosate have been approved, and new risk assessment tools and EU dietary information have been implemented for dietary exposure assessment. Furthermore, the JMPR made an assessment of glyphosate in 2011, which resulted in the setting of a number of new Codex MRLs (CXLs) which were adopted by the EU in 2013. This paper presents a comprehensive assessment of dietary exposure to glyphosate for EU consumers from both domestic and non-domestic food sources. In addition, the global consumer exposure to glyphosate is assessed using the World Health Organization (WHO) Global Environment Monitoring System (GEMS/Food) consumption cluster diets, because trade of commodities treated with glyphosate into and from the EU could lead to different patterns of exposure as a consequence of varying regional diets. The exposure assessments were made on the basis of the current EU and JMPR risk assessment residue definitions; because rape seed, soybeans, maize, and sweetcorn may contain the GAT gene, residue levels are estimated on the basis of a definition of “sum of glyphosate, N-acetyl-glyphosate, AMPA and N-acetyl-AMPA, expressed as glyphosate” (EFSA, 2013). For all other crops, which do not contain the GAT-modification, N-acetyl-glyphosate and N-acetyl-AMPA cannot be formed, and the residue levels for these crops are therefore the sum of glyphosate and AMPA (expressed as glyphosate mass “equivalents”) only. It is noted that the residues of concern defined by the US EPA for the risk assessment of glyphosate do not include the AMPA or N-acetyl-AMPA metabolites. Therefore, exposure estimates made for the North American Free Trade Agreement (NAFTA) region on the basis of the EU/JMPR definition will represent a higher contribution than if based on the components defined as relevant in the US.

Chronic exposure to dietary sources of glyphosate has been estimated using revision 2 of the EFSA Pesticide Residue Intake Model (PRIMo; EFSA, 2006), the German NVS-II and VELS models (BfR, 2012), and the Dutch National Institute for Public Health and the Environment (RIVM) Monte Carlo Risk Assessment (MCRA) probabilistic tool (van der Voet et al., 2014) for pan-Europe and Member State-specific assessments. The WHO GEMS/Food Consumption 17 Cluster Diets IEDI (international estimated daily intake) model (version 2) was used to make global dietary exposure estimates for thirteen regional diets. All estimates were made based on the residues resulting from the critical use patterns that form the basis of the EU MRLs. Although the majority of these use