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

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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

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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.

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[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-acetylglyphosate, 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-acetylglyphosate 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 patterns may relate to the registered uses of glyphosate in the EU, they also incorporate MRLs set by the JMPR and EU on the basis of uses in third countries to which consumers may be exposed as a consequence of the trade of glyphosate-treated food commodities.

This paper provides a comprehensive investigation of dietary exposure to glyphosate using basic and refined assumptions, including probabilistic approaches. Initial estimates were made based on the assumption of residue levels equivalent to EU MRL values without further refinement and using the theoretical maximum daily intake (TMDI) approach defined by the WHO (1989). This estimate was then systematically refined using median residue levels from supervised field trial data (i.e., STMR values) in place of MRLs, processing information and monitoring data in order to achieve a more realistic, deterministic assessment. The current version of PRIMo only allows assessment of intakes in relation to the (notional equivalent total) consumption of raw agricultural commodities and therefore has the potential to overestimate exposure in cases where processing can substantially affect the residue level. Although processing factors can be used, in most cases, these can be applied only to the whole portion of a commodity, both processed and unprocessed. Use of the German models and the WHO IEDI model allows these processing changes to be taken into account for the processed fraction only, providing a more realistic estimate of consumer exposure. Residue-level monitoring data allow further refinements to be made on the basis of actual residue concentration data, obtained through the analysis of produce taken directly from the food chain. This is in contrast to values obtained from supervised residues trials, which are designed to provide information on the highest likely residues according to a particular use pattern.

In contrast to the deterministic assessment methods, which combine a single high-level consumption event with a single measured residue value, probabilistic techniques allow the distribution of intakes amongst individuals within a population to be estimated, taking into account the variability in food consumption between and within individuals and in the occurrence of residues in food commodities (EFSA PPR, 2012). Probabilistic methods are used routinely to assess pesticide exposure in the US; the Dietary Exposure Evaluation Model (DEEM) allows acute probabilistic dietary exposure to be calculated, including specific information about the range and probability of possible exposures. Following recent developments in the EU, both in the assessment of the available methods and the development of computational tools to conduct such assessments, the EFSA Panel on Plant Protection Products and their Residues (PPR) noted in a recent opinion that the probabilistic method is a potentially useful tool for conducting refined consumer exposure assessments (EFSA PPR, 2012). To further refine the estimated glyphosate exposures, probabilistic estimates were made following the EFSA guidance and using the MCRA 8.0 tool developed within the EU-funded Acropolis project (EU, 2015).

The aim of this study, using glyphosate as the test compound, is to apply existing approaches for dietary exposure assessment and review the possible refinements that may be permitted based on data available within the pesticide registration dossier and pesticide residues data collected during EU monitoring activities. The implication of the residue definitions for enforcement and risk assessment are considered, together with the use of conversion factors. A comparison of exposures using deterministic and probabilistic approaches is made and the implications of the varying approaches, in terms of the estimated exposures, are discussed. The study focusses on the exposure to residues of glyphosate and its potential metabolites through the diet and does not consider formulation components which are outside the scope of the approaches taken.

2. Materials and methods

2.1. Theoretical maximum daily intake (TMDI) calculation

The TMDI for glyphosate was estimated using revision 2 of the EFSA Pesticide Residue Intake Model (PRIMo). Existing MRLs, as established in Commission Regulation (EU) No. 293/2013, were used as residue input values based on residues of glyphosate only—i.e., the definition of residue for enforcement in the EU for non-tolerant crops, because the 2015 EFSA conclusion states that the contribution of AMPA to consumer exposure is minor and a conversion factor is unnecessary (EFSA, 2015b). For tolerant crops, the conversion factors in Table 1 were applied to take account of the possible presence of metabolite residues. The ratio of metabolites in products of animal origin is dependent on the ratios in animal feed; therefore, conversion factors were estimated based on the conversion factors derived for the feed items and the relative worst-case contribution of these to the total animal diet (as defined by the OECD, 2013). The intakes were calculated for all of the 27 EU population diets, including nine diets for infants and children, for which consumption data are currently available. The calculation was not refined to take account of any modification of residue levels as a result of processing.

2.2. Refined chronic dietary intakes

The national estimated daily intake (NEDI) was calculated, using PRIMo for the 27 EU representative diets, by replacing MRL values with the appropriate supervised trials median residue (STMR) levels where available. Unlike the MRLs, which are based on a definition of glyphosate only, the STMRs are based on the relevant definition for risk assessment: the sum of glyphosate, N-acetyl-glyphosate, AMPA and N-acetyl-AMPA, expressed as glyphosate. The STMRs were obtained from public documents, including EFSA reasoned opinions on MRLs (as cited in Table 2), the glyphosate draft assessment report (DAR; Germany, 1998) and the renewal assessment report (RAR; Germany, 2013). In addition, because some EU MRLs are based on uses in third countries, further STMR data were obtained from JMPR Reports (WHO/FAO, 2005, 2011). The STMR values represent the median value from supervised residues trials conducted according to the use pattern (good agricultural practice; GAP) on which the EU MRL is based.

N-acetyl-glyphosate and N-acetyl-AMPA form only in crops that contain the GAT gene (potentially rape seed, soya bean, maize, and sweetcorn; although these are not commercially available at the time of writing[2]), and therefore, the residues in all other crops, whether conventional or transgenic (ESPS or GOX genes) comprise only glyphosate and AMPA. This assessment assumes that the diet could contain up to 100% modified crops and therefore assesses the exposure to all four components of the definition for rape seed, soya bean, and maize, and the exposure to glyphosate and AMPA (since N-acetyl-glyphosate and N-acetyl-AMPA are not present) for all other crops in the diet. The EU MRL for sweetcorn is set based on the use on an EPSPS variety. As such, the STMR value is based on glyphosate and AMPA only. A summary of the STMR values used for the chronic intake assessment are given in Table 2. Where there is no expected or known use of glyphosate, or no information is available on the expected residue levels, the default MRL value has been included instead.

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[2] Rape seed (canola) is currently at Phase 4 (pre-launch) of the R&D pipeline: http://www.pioneer.com/CMRoot/Pioneer/About_Global/our_research/pipeline/spec_sheets/spec_sheets_files/Canola_HerbicideTolerance_2015.pdf.

Table 1
Conversion factors used in the TMDI calculation.

Product of plant origin	Conversion factor (median)	Source	Product of animal origin	Conversion factor	Livestock diet (S:R:M ratio[a])
Sweet corn	3.0	USA import tolerance EFSA, 2009b	Swine tissues	12.0	Finishing swine (60:35:5)
Rape seed	9.4	USA import tolerance EFSA, 2013	Bovine, goat, horse and other farmed animal tissues	10.0	Beef cattle (40:30:30)
Soya bean	17.7	USA import tolerance EFSA, 2009b	Sheep tissues	13.1	Ram/ewe (55:45:0)
Maize/corn	3.0	USA import tolerance EFSA, 2009b	Poultry tissues and eggs	12.4	Turkey (60:38:2)
			Milk	9.7	Dairy cattle (35:30:35)

[a] Ratio of soya bean (S), rapeseed (R) and maize (M) based feed items – conversion factors of 9.4, 17.7 and 3.0, respectively.

Table 2
STMR values used for estimation of chronic dietary intake.

Crop or crop group	Residue level (mg/kg)	Source[a]	Crop or crop group	Residue level (mg/kg)	Source
Citrus fruit	0.05	STMR: RAR, 2013	Mustard seed	10	EU MRL: EC, 2013
Tree nuts	0.05	STMR: RAR, 2013	Cotton seed	1.4	STMR: DAR, 1998
Pome fruit	0.05	STMR: RAR, 2013	Oilseeds (except those listed above)	0.05	STMR: RAR, 2013
Stone fruit	0.05	STMR: RAR, 2013	Olives for oil production	0.19	STMR: RAR, 2013
Table and wine grapes	0.05	STMR: DAR, 1998	Oil fruits (except olives)	0.1	EU MRL: EC, 2013
Strawberries	0.05	STMR: RAR, 2013	Barley, oats	5.85	STMR: RAR, 2013
Cane fruit	0.1	EU MRL: EC, 2013	Rye, wheat	1.18	STMR: DAR, 1998
Other small fruits and berries	0.1	EU MRL: EC, 2013	Sorghum	4.61	STMR: DAR, 1998
Miscellaneous fruit (except table olives and bananas)	0.1	EU MRL: EC, 2013	Maize	0.12	STMR: EFSA, 2009a,b
Table olives	0.19	STMR: RAR, 2013	Buckwheat, millet, rice, other cereals	0.05	STMR: RAR, 2013
Bananas	0.05	STMR: JMPR, 2005	Tea	0.23	STMR: DAR, 1998
Potatoes	0.155	STMR: DAR, 1998	Coffee beans, cocoa, carob	0.1	EU MRL: EC, 2013
Tropical root and tuber vegetables	0.05	STMR: RAR, 2013	Herbal infusions	0.05	STMR: RAR, 2013
Other root and tuber vegetables except sugar beet	0.05	STMR: RAR, 2013	Hops	0.1	EU MRL: EC, 2013
Bulb vegetables	0.05	STMR: RAR, 2013	Spices	0.1	EU MRL: EC, 2013
Solanacea	0.05	STMR: RAR, 2013	Sugar beet (root)	3.4	STMR: JMPR, 2011
Cucurbits – edible peel	0.05	STMR: RAR, 2013	Sugar cane	0.27	STMR: JMPR, 2005
Cucurbits – inedible peel	0.05	STMR: RAR, 2013	Chicory roots, other sugar plants	0.05	STMR: RAR, 2013
Sweetcorn	0.325	STMR: JMPR, 2011	Swine meat, fat, liver	0.125	STMR: RAR, 2013
Brassica vegetables	0.05	STMR: RAR, 2013	Swine kidney	0.059	STMR: RAR, 2013
Leaf vegetables and fresh herbs	0.05	STMR: RAR, 2013	Swine edible offal, other swine products	0.05	EU MRL: EC, 2013
Legume vegetables	0.05	STMR: RAR, 2013	Bovine meat	0.125	STMR: RAR, 2013
Stem vegetables	0.05	STMR: RAR, 2013	Bovine fat	0.131	STMR: RAR, 2013
Cultivated fungi	0.1	EU MRL: EC, 2013	Bovine liver	0.11	STMR: RAR, 2013
Wild fungi	3.58	STMR: DAR, 1998	Bovine kidney	0.31	STMR: RAR, 2013
Beans (dry)	0.17	STMR: JMPR, 2005	Bovine edible offal, other bovine products	0.05	EU MRL: EC, 2013
Lentils (dry)	1.48	STMR: EFSA, 2012	Sheep, goat, horse and other farm animals meat, fat, liver, kidney, edible offal	0.05	EU MRL: EC, 2013
Peas, lupins (dry)	0.38	STMR: DAR, 1998	Poultry meat, fat, liver	0.125	STMR: RAR, 2013
Other pulses (dry)	0.1	EU MRL: EC, 2013	Poultry kidney	0.155	STMR: RAR, 2013
Linseed	2.15	STMR: DAR, 1998	Poultry edible offal, other poultry products	0.05	EU MRL: EC, 2013
Sunflower seed	1.24[b]	STMR: DAR, 1998	Milk and milk products	0.05	STMR: RAR, 2013
Rape seed	3.15	STMR: EFSA, 2013	Eggs	0.04	STMR: RAR, 2013
Soya bean	2.2	STMR: EFSA, 2009a,b	Honey	0.05	EU MRL: EC, 2013

[a] JMPR refers to the Joint Meeting on Pesticide Residues (WHO/FAO).
[b] Sum of glyphosate STMR (DAR, 1998) and a maximum 10% contribution from AMPA (JMPR, 2005): 1.13 + 0.11 = 1.24 mg/kg.

2.3. Further refinements of chronic dietary intakes using processing information and monitoring data

The analysis of glyphosate has been included in the EU co-ordinated monitoring programme and in some individual Member State (MS) national monitoring programmes for a number of years. Where available, mean residue values derived from European monitoring surveys have been used in place of MRL and STMR values to give a more realistic, albeit retrospective, estimate of exposure to glyphosate. These residue levels are considered more realistic, because they are samples obtained in the food chain where residues have been subject to changes in levels as a result of actions such as transportation and storage prior to consumption. Furthermore, the monitoring data reflect that all samples may not have been treated with glyphosate, or may not have been treated according to the maximum permitted application rates. Conversion factors have been applied to monitoring results based on the analysis of glyphosate only where metabolite residues may be expected. A median conversion factor (CF) of 1.05 for lentils was derived by EFSA (2012) for estimating residues according to the risk assessment definition (glyphosate and AMPA) from the enforcement definition (glyphosate only). A CF of 1.1 has also been applied to oats, rye, and wheat to cover the potential contribution from AMPA (RAR, 2013). The refined input values from the monitoring, taking into account the relevant residue definition, are summarised in Table 3.

Where a commodity is predominantly consumed in a processed form, processing factors (PF) have been applied to the residue measured in the raw agricultural commodity to take account of the loss or transformation of residues during commercial processing practices. Furthermore, where a commodity may be consumed in various forms (e.g., whole fruit or fruit juices), and consumption data are available for the processed commodities; processing factors have also been used. If processing information was not available for specific commodities, processing factors for similar products have been used analogously, or the residue measured in the raw commodity (RAC) was entered. Table 4 gives a summary of the available processing information used to refine the dietary intake estimation.

Barley is a significant contributor to the critical (highest intake) diet in the EFSA PRIMo for the refined assessment (Irish adult; 1.5% ADI), so a breakdown of the consumption data at a lower level of aggregation for the Irish adult diet was obtained from an EFSA Reasoned Opinion (2009a) to further refine the intakes for this commodity using the processing factors in the table above. These extended consumption data are provided in Table 5.

These refinements have been applied as far as possible depending on the presentation of the consumption data, and used to make refined deterministic assessments of the chronic exposure to glyphosate using the national German NVS-II (German adult diet) and VELS (German child diet) models, the pan-European EFSA PRIMo, and the global WHO GEMS/Food Consumption 17 Cluster Diets IEDI model (covering global regional diets).

2.4. Probabilistic dietary intake assessment

MCRA 8.0 was used to model chronic dietary exposure to glyphosate using a probabilistic approach. MCRA 8.0 is a research tool that implements many possibilities for modelling single compound or cumulative exposure, including the procedures described in the EFSA guidance for acute or chronic exposure assessment according to both an optimistic and a pessimistic model run (van der Voet et al., 2014).

UK monitoring data, from the Defra Expert Committee on Pesticide Residues in Food (PRiF) surveillance programmes (2011–2014), were used to provide concentration information for glyphosate residues in foodstuffs. The EU MRLs were also entered to supplement concentration data for food commodities which had not been included in the PRiF surveillance activities (pessimistic scenario only). A summary of the UK monitoring data is given in Table 6.

Probabilistic exposure was determined separately for children and adults. The adult food consumption data used were those of the Dutch National Food Consumption Survey (DNFCS) of 2003 (Ocké et al., 2005). In this survey, 750 persons aged 19–30 years were asked about their eating habits via two independent, computerised 24-h dietary recalls, with the repeated recall within 7–14 days of the first recall and on another day of the week. The child food

Table 3
Summary of glyphosate residues from EU monitoring activities.

Commodity	Number samples analysed	No samples containing detectable residues	Range of residues (mg/kg)	Mean glyphosate residue (mg/kg)	Mean risk assessment residue (mg/kg)	Source
Mandarin (extrapolated to citrus fruit[a])	Not reported	Not reported	Not reported	0.022	0.022[b]	The 2013 European Union report of pesticide residues in food (EFSA, 2015a)
Apples	Not reported	Not reported	<0.036	0.023	0.023[b]	The 2013 European Union report of pesticide residues in food (EFSA, 2015a)
Table grapes	Not reported	Not reported	Not reported	0.021	0.021[b]	The 2013 European Union report of pesticide residues in food (EFSA, 2015a)
Wine grapes (wine)	55	5	<0.37	0.155	0.155[b]	The 2013 European Union report of pesticide residues in food (EFSA, 2015a)
Cauliflower	110	1	<0.09	0.054	0.054[b]	The 2012 European Union report of pesticide residues in food (EFSA, 2014b)
Beans (with pods)	Not reported	Not reported	Not reported	0.013	0.013[b]	The 2012 European Union report of pesticide residues in food (EFSA, 2014b)
Lentils (dry)	54	16	<0.1–2.7	0.267	0.280 (0.267 × 1.05 conversion factor)	The Expert Committee on Pesticide Residues in Food report on the Pesticides Residues Monitoring for Quarter 4 2011 (PRiF, 2011)
Oats	124	55	<1.5	0.382	0.420 (0.382 × 1.1 conversion factor)	The 2013 European Union report of pesticide residues in food (EFSA, 2015a)
Rice				0.050	0.050	The 2011 European Union report of pesticide residues in food (EFSA, 2014a)
Rye	242	12	<2.06	0.195	0.215 (0.195 × 1.1 conversion factor)	The 2013 European Union report of pesticide residues in food (EFSA, 2015a)
Wheat	Not reported	Not reported	Not reported	0.081	0.089 (0.081 × 1.1 conversion factor)	The 2013 European Union report of pesticide residues in food (EFSA, 2015a)

"<" = residues up to … (full range of residues values or the limit of quantitation not reported).

[a] The residue for mandarin has been extrapolated to the whole group of citrus. Citrus fruit are treated around the base of the tree and therefore residues are expected to be low and consistent across the group, with smaller varieties, such as mandarins, representing a worst case.

[b] No AMPA residues expected as glyphosate is the predominant residue in these crops (DAR, 1998).

Table 4
Summary of processing data and refined input values for glyphosate.

RAC	Processed commodity	PF	Input value (mg/kg)	Source
Citrus fruit	*Whole fruit*		*0.022*	RAR, 2013
	Juice	0.83	0.018	Based on glyphosate only, residues of AMPA were <LOQ[a].
	Peel	3	0.066	[German & WHO model inputs only]
Rape seed	*Unprocessed seed*		*3.15*	EFSA, 2013
	Refined oil	<0.01	<0.032	Based on total residue definition for risk assessment.
Soya bean	*Unprocessed seed*		*2.2*	WHO/FAO, 2005
	Crude oil	<0.02	0.044	Based on glyphosate + AMPA, according to the STMR definition [German & WHO model inputs only]
Cotton seed	*Unprocessed seed*		*1.4*	WHO/FAO, 2005
	Refined oil	<0.1	0.14	Based on glyphosate + AMPA, according to the STMR definition
Olives for oil production	*Whole fruit*		*0.19*	RAR, 2013
	Olive oil, refined	0.22	0.042	Based on glyphosate only, residues of AMPA were <LOQ.
Barley	*Unprocessed grain*		*5.85*	Harris and Gaston, 2004
	Beer	0.03	0.176	Based on glyphosate only
	Malt	0.16	0.936	
Maize	*Unprocessed grain*		*0.12*	WHO/FAO, 2005
	Flour	1.1	0.132	Based on glyphosate + AMPA, according to the STMR definition
	Oil	<0.33	<0.04	[WHO model input only]
Oats	*Unprocessed grain*		*0.42*	WHO/FAO, 2005
	Oats, rolled	0.2	0.084	Based on glyphosate + AMPA, according to the STMR definition [WHO model input only]
Rye	GLY:			RAR, 2013
	Unprocessed grain		*0.195*	AMPA residue of 0.02 estimated from monitoring result of 0.195 mg/kg glyphosate, assuming a CF of 1.1
	Flour	0.44	0.086	
	Bran	1.5	0.293	[German & WHO model inputs only]
	AMPA:			
	Unprocessed grain		*0.020*	
	Flour	1.3	0.026	
	Bran	0.76	0.015	
	TOTAL:			
	Flour		0.112	
	Bran		0.308	
Sorghum	*Unprocessed grain*		*4.61*	WHO/FAO, 2005
	Flour	0.32	1.48	Based on glyphosate + AMPA, according to the STMR definition [WHO model input only]
Wheat	GLY:			RAR, 2013
	Unprocessed grain		*0.081*	AMPA residue of 0.008 estimated from monitoring result of 0.081 mg/kg glyphosate, assuming a CF of 1.1
	Flour	0.57	0.046	[German & WHO model inputs only]
	Bran	1.8	0.146	
	AMPA:			
	Unprocessed grain		*0.008*	
	Flour	0.81	0.006	
	Bran	1.2	0.010	
	TOTAL:			
	Flour		0.052	
	Bran		0.156	
	GLY:			WHO/FAO, 2005
	Unprocessed grain		*0.089*	Based on glyphosate + AMPA, according to the STMR definition
	Bread	0.32	0.032	[WHO model input only]
Sugar beet	*Unprocessed root*		*3.4*	WHO/FAO, 2011
	Sugar, refined	<0.01	0.034	Definition not stated
Sugar cane	*Unprocessed cane*		*0.27*	WHO/FAO, 2005
	Cane sugar, refined	<0.24	0.065	Based on glyphosate + AMPA, according to the STMR definition

[a] Limit of quantification (LOQ).

Table 5
Chronic consumption data for barley in the Irish adult diet.

Diet	Food as consumed		Food intake as consumed (g/kg bw/d)
Irish (IE) Adult (Body weight = 75.2 kg)	Code 0500010	Barley	1.2407
		Barley from breakfast cereals	0.0650
		Barley from lager	4.1300
		Barley from stout	7.4650
		Barley from malt	0.2550

consumption data were those of the 2005/2006 DNFCS — Young Children survey (Ocké et al., 2008). In this survey, 1279 children, aged 2–6 years, were surveyed by dietary record over three days.

To link the food consumption data to the raw agricultural commodities (RACs) for which concentration data and MRLs information were available, a conversion database was used. The database was developed as part of the EFSA project, “Development of a database of conversion factors to transform foods coded according to FoodEx into RACs, NP/EFSA/DATEX/2010/02”. In this conversion database, FoodEx1 codes, used to describe the consumption data, were linked to their RAC ingredients, including weight percentages, based on information in the Dutch food conversion database (Boon et al., 2009; van Dooren et al., 1995).

Basic optimistic and pessimistic exposure scenarios were run according to the EFSA guidance (EFSA PPR, 2012), based on both the Netherlands adult and young child dietary information and the

Table 6
UK monitoring data for glyphosate (2011–2014).

Foodstuff	Number of samples	Number of samples with residues ≥ LOQ[a]	Range of residues (mg/kg)
Other grains	74	35	0.1–3.2
Oats, grain	65	54	0.1–1.5
Rice	72	1	0.1
Wheat flour, brown	3	1	0.2
Wheat flour, white	126	2	0.1–0.2
Wheat flour, wholemeal	233	64	0.1–1.1
Bread and rolls	128	6	0.1–0.2
Wheat bread, white	196	32	0.1–0.2
Wheat bread, with bran	167	73	0.1–1.3
Rye bread and rolls	4	0	–
Multigrain bread and rolls	74	14	0.1–0.4
Pita bread	13	1	0.3
Tortilla	35	1	0.2
Noodle	36	1	0.2
Cereal bars	48	11	0.1–0.3
Croissant	3	0	–
Pancakes	3	0	–
Scone	4	0	–
Waffles	2	0	–
Brioche	10	0	–
Legumes, beans dried	34	3	0.3–1.1
Beans	67	16	0.2–2.7
Lentils	84	19	0.1–2.7
Soya bean flour	3	0	–
Soya drink	84	0	–
Beer and beer-like beverage	54	1	0.1
Cereal-based food for infants	13	0	–

[a] Limit of quantification (LOQ): 0.1 mg/kg.

Table 7
Modelling parameters for basic optimistic and pessimistic chronic dietary exposure assessment.

Assessment component	Optimistic scenario	Pessimistic scenario
Concentration model	EFSA guidance optimistic	EFSA guidance pessimistic
Modelling consumption	Observed individual means method + bootstrap	Observed individual means method + bootstrap. Upper tail drill-down analysis
Unmeasured residues in animal commodities	Zero	MRL
Treatment of residues below LOR (limit of reporting)	Treat as zero	Set at LOR
No monitoring data	Assume no residues	Use MRL
Residues in water	Zero	Assume legal limit (0.1 ppb)
Uncertainty analysis	Empirical, 100 resample cycles	
Uncertainty bounds	2.5%, 97.5%	
Drill-down percentage[a]	No drill-down	97.5%

[a] Defines the% of the upper tail of the distribution (upper 2.5%) within which exposure estimates are considered in greater detail to ensure that the results are realistic (contributing foods, amounts consumed, and residue levels). The information from the upper tail can be useful for targeting risk mitigation measures if required.

parameters detailed in Table 7.

3. Results

3.1. Deterministic assessments of chronic dietary intake according to the EFSA PRIMo

3.1.1. Theoretical maximum daily intake (TMDI)

Intakes were initially calculated using the TMDI approach, which combines mean consumption levels with the MRL for each commodity, sums these intakes for all commodities, and expresses the result on a consumer body-weight basis. Conversion factors were also used to take account of the possible contribution of metabolites, because the MRL values are based on a residue definition of glyphosate only. The mean body weights for each consumer population included in the EFSA PRIMo rev. 2 were used. A TMDI value is calculated for each of the different consumer populations and population sub-groups in the model, and is expressed in units of mg/kg bw/day. The dietary exposure assessment compares the intake to the acceptable daily intake (ADI), which is the relevant toxicity reference dose for chronic risk assessment. The most exposed population was found to be the UK toddler group, with intakes accounting for 80.1% of the ADI of 0.5 mg/kg bw/day. The commodities contributing the highest proportion to the UK toddler intakes were sugar beet (root), wheat, and milk and cream, accounting for 68.6%, 7.8%, and 2.0% of the intake, respectively.

As noted in Table 4, sugar beet is not consumed raw, but rather, is consumed primarily as sugar, following extensive processing, and this process leads to a reduction in residues by a factor of <0.01. If the MRL is converted to the MRL-P (the maximum residue expected in sugar) the residue would be expected to be below 0.15 mg/kg, and the resulting intakes of sugar for the UK toddler are reduced to 0.7% ADI. Mean sugar beet consumption by the UK toddler is 331.6 g/day (assuming an average body weight of 14.5 kg) (EFSA PRIMo rev. 2; data source, Gregory et al., 1995). Based on information from British Sugar, this would be equivalent to approximately 57 g sugar per day,[3] which is three times higher than the WHO recommendation for children aged four to six (based on 5% of daily energy intake; WHO, 2015). A more recent UK dietary survey shows that, in 2008–2012, the consumption of sugar by toddlers (1.5–3 years old) has reduced to 36.1 g per day (NDNS, 2014). Based on glyphosate residues of 0.15 mg/kg in sugar, intakes would account for less than 0.1% ADI based on the 2008–2012 toddler consumption values.

3.1.2. National estimated daily intake (NEDI)

To estimate a realistic exposure scenario, the TMDI calculation was refined to take account of STMR values, monitoring data, and processing information. The NEDI, based on the substitution of MRLs for STMR values, where available, reduced the maximum intake to 16.8% ADI (UK Toddler). The STMR values used in this estimation were based on the appropriate residue definition for risk assessment for the commodities to which glyphosate may be applied. Applying the processing factor for sugar, made from sugar

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[3] “On average one hectare of sugar beet crop yields about 41 tonnes of clean, topped root from which seven tonnes of sugar can be extracted”; British Sugar, 2010, www.britishsugar.co.uk/Files/...a-Sugar.../inside_a_sugar_factory.aspx.

beets, further reduces the total intakes to 3.6% ADI for the WHO Cluster diet B, with wheat, barley and soya bean accounting for 2.0%, 0.3%, and 0.3% of the total intake, respectively.

3.1.3. *Refined national estimated daily intake*

The NEDI was refined in two further steps: substitution of STMR values for actual residues found in the monitoring data (Table 3) and extended use of processing information (Table 4) to commodities other than sugar beet in order to consider the residues present in the food as consumed. Following these steps, the most exposed population is the Irish adult with intakes accounting for 2.1% ADI, of which barley accounts for 1.5%, potatoes 0.1%, and linseed 0.1%. This assessment was refined further, taking into account intakes for barley according to the commodities as consumed (Table 5), rather than the raw agricultural commodity. This additional refinement reduced the contribution from barley to 0.53% (see Table 8) and the overall chronic dietary exposure to 1.2% ADI.

3.2. *Deterministic assessments of chronic dietary intake according to the German NVS-II and VELS model*

3.2.1. *Refined chronic dietary intake — Germany*

Using the same residue inputs for the refined NEDI above, but with additional information on the processing of citrus and cereals, the chronic dietary intake for the German child (2–4 years; VELS-model) and the general population (14–80 years; NVS-II-model) were calculated (see Table 9). Intakes for adults were up to 1.3% of the ADI, and for children, up to 1.2% of the ADI (assuming an average body weight). The major contributors to the diet were sunflower seeds for children (0.3%) and barley, processed (0.6%) for adults. No processing information is available for the transfer of residues to sunflower oil, although the behaviour with other oilseeds suggests a dilution and therefore a lower exposure than that presented here. Similarly for barley, processed, 58% of this intake is from beer, for which residues are known to be lower by a factor of 0.03, than in the RAC.

Intakes of glyphosate calculated for the focal consumer groups for the UK toddler, German child, and Irish adult (including the TMDI, NEDI and refined NEDIs) are presented in Fig. 1. Summary results of the deterministic dietary exposure assessments are provided in Table 10.

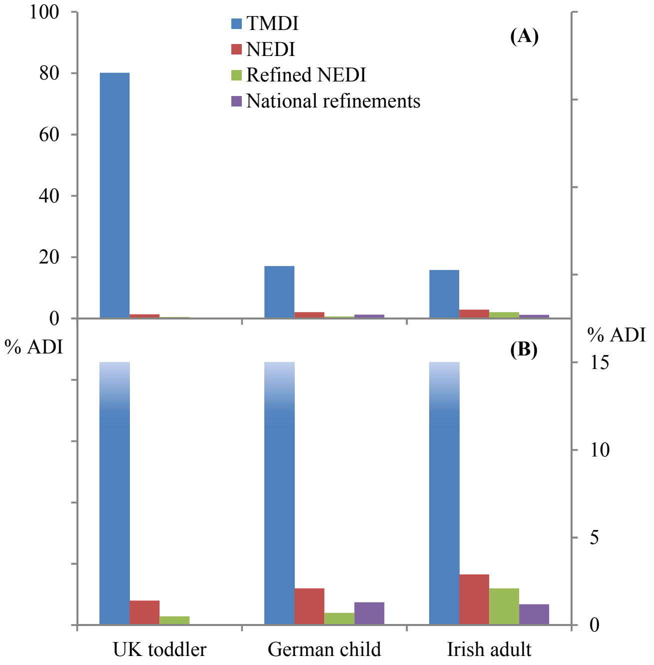

Fig. 1. Intakes of glyphosate (in% ADI) for the focal consumer groups overall (A) and within the truncated range 0–15% ADI (B). [Note: intake assessments were performed using PRIMo rev. 2 except for the German child national refinements which used the German VELS model. National refinements for Ireland used the consumption data in Table 5].

Table 8
Refined dietary intakes (NEDI) for processed barley commodities (Irish adult diet).

Commodity	Consumption value (g/kg bw/d)	Residue (mg/kg)	Intake (mg/kg bw/d)	Intake (% ADI)
Consumption as barley				
Barley, unprocessed	1.2407	5.85 (STMR)	0.00726	1.45
Consumption as barley processed commodities				
Barley from breakfast cereals	0.0650	5.85 (STMR)	0.00038	0.076
Barley from lager	4.1300	0.176 (STMR-P: beer)	0.00073	0.15
Barley from stout	7.4650	0.176 (STMR-P: beer)	0.00131	0.26
Barley from malt	0.2550	0.936 (STMR-P: malt)	0.00024	0.048
Total processed barley			**0.00265**	**0.53**

Table 9
Deterministic estimates of chronic dietary exposure to glyphosate using the German NVS-II and VELS model.

Chronic dietary exposure assessments: Glyphosate (ADI = 0.5 mg/kg bw/d)							
	Children (2–4 years) [VELS-model]	Average body weight (bw)	Individual consumption/bw ratio	General population (14–80 years) [NVS-II-model]	Average body weight (bw)	General population (14–80 years) [NVS-II-model]	Individual consumption/bw ratio
	Intake (mg/kg bw/d)	0.0065	0.0069	Intake (mg/kg bw/d)	0.006	Intake (mg/kg bw/d)	0.0066
	Intake (% ADI)	1.3%	1.4%	Intake (% ADI)	1.2%	Intake (% ADI)	1.3%
Highest contributors	Sunflower seeds, total	0.3%	0.4%	Barley, processed	0.6%	Barley, processed	0.6%
	Oat, bran	0.2%	0.2%	Sunflower seeds, total	0.2%	Sunflower seeds, total	0.2%
	Milk, cream, butter and other fats	0.2%	0.2%	Milk, cream, butter and other fats	0.1%	Milk, cream, butter and other fats	0.1%
	Potatoes	0.1%	0.1%	Potatoes	0.0%	Oat, bran	0.1%
	Apples, portion in juice	0.0%	0.0%	Wheat, processed	0.0%	Potatoes	0.0%

Table 10
Deterministic estimates of chronic dietary exposure to glyphosate using EFSA PRIMo.

Chronic dietary exposure assessments: Glyphosate (ADI = 0.5 mg/kg bw/d)							
Calculated intake in% ADI	Member state (MS) diet	1st contributor to MS diet (% ADI)	Commodity	2nd contributor to MS diet (% ADI)	Commodity	3rd contributor to MS diet (% ADI)	Commodity
TMDI (MRLs)							
80.1	UK Toddler	68.6	Sugar beet (root)	7.8	Wheat	2.0	Milk and cream
71.2	WHO Cluster diet B	43.0	Soya bean	17.1	Wheat	3.0	Sunflower seed
68.6	WHO Cluster diet E	41.1	Soya bean	11.2	Rape seed	7.9	Wheat
66.0	WHO Cluster diet F	46.1	Soya bean	7.2	Wheat	5.9	Rape seed
45.5	WHO Cluster diet D	26.1	Soya bean	13.0	Wheat	2.0	Sunflower seed
NEDI (with STMR replacement of MRLs)							
3.6	WHO Cluster diet B	2.0	Wheat	0.3	Barley	0.3	Soya bean
3.3	WHO Cluster diet E	0.9	Barley	0.9	Wheat	0.4	Rape seed
3.0	DK Child	1.3	Wheat	1.0	Rye	0.5	Oats
2.9	IE Adult	1.5	Barley	0.5	Wheat	0.2	Oats
2.8	WHO Cluster diet F	0.8	Wheat	0.7	Barley	0.3	Soya bean
Refined NEDI (with processing and monitoring data)							
2.1	IE Adult	1.5	Barley	0.1	Potatoes	0.1	Linseed
1.8	WHO Cluster diet E	0.9	Barley	0.3	Soya bean	0.1	Potatoes
1.5	WHO Cluster diet B	0.3	Barley	0.3	Soya bean	0.2	Sunflower seed
1.5	WHO Cluster diet F	0.7	Barley	0.3	Soya bean	0.1	Potatoes
1.0	WHO Cluster diet D	0.3	Barley	0.2	Soya bean	0.1	Potatoes

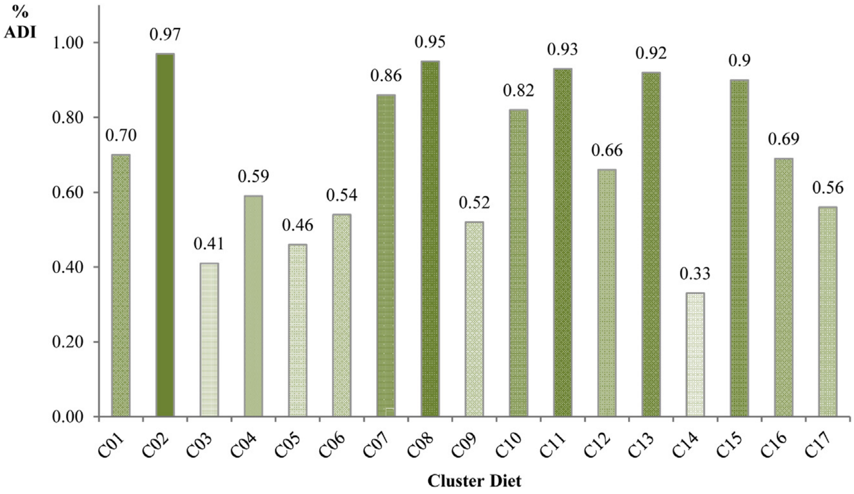

Fig. 2. International Estimates of Daily Intake of glyphosate (in % ADI) for the WHO GEMS/Food 17 Cluster Diets. Details of the geographical distribution of each of the WHO GEMS/Food Clusters are shown in Fig. 3.(WHO, 2012).

3.3. Deterministic assessments of chronic dietary intake according to the WHO GEMS/Food 17 cluster diets IEDI model (version 02)

3.3.1. Refined international estimated daily intake (IEDI)

A refined IEDI was estimated from the dietary information in the WHO GEMS/Food 17 Cluster Diets IEDI Model (v2) and the concentration data and processing information summarised in Tables 2–4 Intakes, in terms of % ADI, are summarised in Fig. 2 and ranged from 0.33% to 0.97% for the cluster diets C14 and C02, respectively.[4] Fig. 3 shows the global predicted exposure to glyphosate, with countries having a higher exposure represented by a darker colour. Overall, the predicted intakes are lower than based on the EU models, which may reflect the greater degree of refinement for processing permitted by this model. The highest commodity intake for the critical diet (Cluster C02) was for sunflower at 44.47 μg/person/day of which is almost exclusively (>99%) consumed as oil. Processing data are not available for sunflower oils, which, based on the reduction of residues following oil production for other oilseeds and fruits, could have led to further refinement of the estimated intakes.

3.4. Probabilistic dietary intake assessment

The chronic probabilistic exposure to glyphosate was calculated for the Dutch adult and child based on monitoring data collected between 2011 and 2014 in the UK. Only the UK national surveillance programme routinely analyses for glyphosate in multiple commodities and reports the results in detail. The samples are typically taken from the market and are representative of both national, EU and non-EU origin production. Therefore these data are likely to be representative of similar commodities on the market in other EU countries, such as the Netherlands. For the optimistic scenario, intakes were based only on the commodities sampled in the UK surveillance programme and were treated as zero where no residue data were available. In the pessimistic scenario, gaps in the concentration data for both plant and animal

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[4] Cluster C14: Comoros, Fiji Islands, Kiribati, Papua New Guinea, Solomon Islands, Sri Lanka and Vanuatu. Cluster C02: Albania, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, Republic of Moldova and Ukraine.

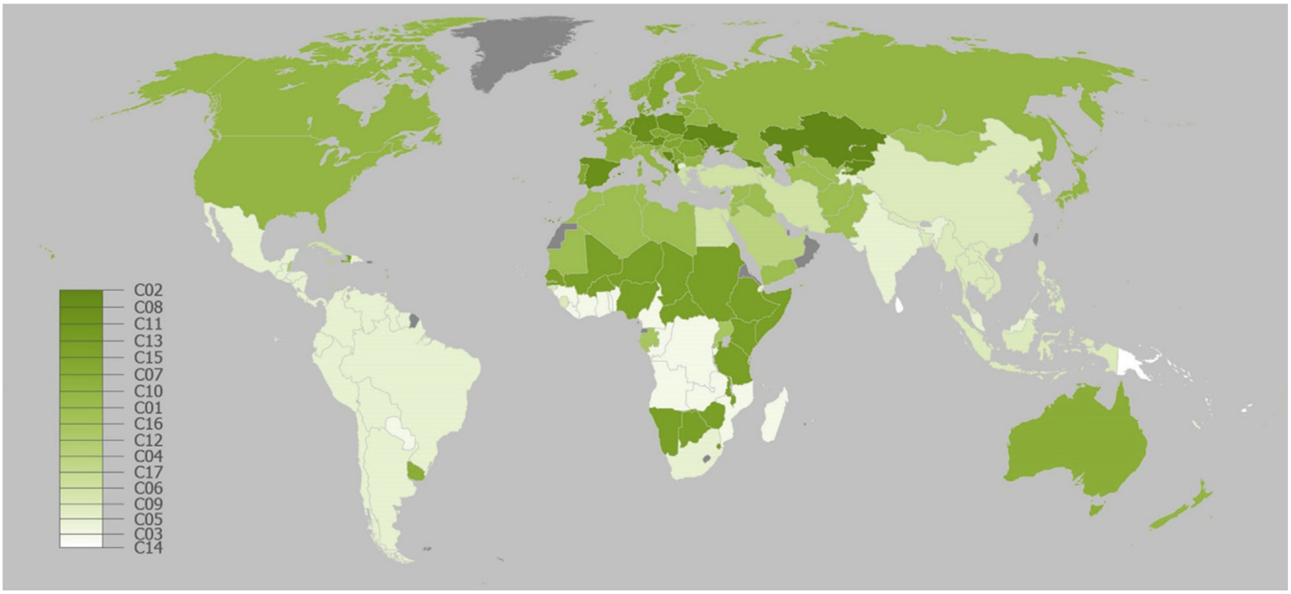

Fig. 3. World map of glyphosate intakes (ranked by% ADI) for the WHO GEMS/Food 17 Cluster Diets and based on residue levels from EU and JMPR assessments. Note: The input values for this assessment are EU and JMPR residue endpoints (MRLs and median residues), as detailed in Tables 2–4, and include EU and JMPR processing information where applicable. The assessment is not based on residues arising in the assessed countries. Each cluster (C) is ranked from 1 through 13, based on the ascending% ADI accounted for by the intakes of that region. Ascending ranks are represented by a darker coloration for that area—e.g., Cluster C14 intakes account for 0.33% ADI and are assigned rank 1 and coloured white; Cluster C02 has the highest intakes of 0.97% ADI and is represented by the darkest shade of green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

commodities were replaced by the corresponding EU MRL. The number of person-days per million exceeding levels of exposure equivalent to 1%, 10%, 50%, 100%, 200%, and 500% of the ADI for each scenario are given in Table 11. For the adult diet, no individuals were found to have intakes above 1% ADI based on either the optimistic or pessimistic assumptions made according to the EFSA guidance (EFSA PPR, 2012). For the young child's diet, the optimistic model run again shows that no individuals would be expected to have intakes exceeding 1% ADI, whereas in the pessimistic model run, 155 people per million had a predicted exposure above 1% ADI, with an upper confidence limit of 1715, but none were above 10% ADI.

The 99.9 percentile (P99.9) of chronic exposure for each of the exposure scenarios is given in Table 12. The figures demonstrate that the assumptions made in the pessimistic scenario, including the use of MRLs as surrogate values where monitoring data are not available, make a high contribution to the overall exposure. The P99.9 exposure for the Netherlands child for the pessimistic model run is 0.90% of the ADI. None of the alternative scenarios leads to a P99.9 exposure above 1% ADI, even at the upper confidence limit.

The top three commodities contributing to the exposure for the Dutch child in the pessimistic run were apples, bread and rolls, and

Table 12
P99.9 level of chronic dietary exposure (μg/kg bw/day) for Dutch young child and adult.

Diet	Scenario	Exposure (μg/kg bw/day)	Lower bound (p2.5)	Upper bound (p97.5)	% ADI
Child	Optimistic	0.64	0.25	1.33	0.13
	Pessimistic	4.49	3.80	4.85	0.90
Adult	Optimistic	0.17	0.11	0.26	0.03
	Pessimistic	2.89	1.56	2.92	0.58

Table 11
Probabilistic chronic dietary exposure to glyphosate for the Dutch child and adult.

Exposure levels			Number of person-days per million exceeding exposure level (lower bound p2.5 – upper bound p97.5)	
Exposure (μg/kg bw/day)	% of ADI	Margin of exposure	Optimistic	Pessimistic
Dutch Young Child (2–6 years)				
5	1	10,000	0 (0–0)	155 (0–1715)
50	10	10,000	0 (0–0)	0 (0–0)
250	50	200	0 (0–0)	0 (0–0)
500	100	100	0 (0–0)	0 (0–0)
1000	200	50	0 (0–0)	0 (0–0)
2500	500	20	0 (0–0)	0 (0–0)
Dutch Adult				
3	1	10,000	0 (0–0)	0 (0–0)
30	10	10,000	0 (0–0)	0 (0–0)
150	50	200	0 (0–0)	0 (0–0)
300	100	100	0 (0–0)	0 (0–0)
600	200	50	0 (0–0)	0 (0–0)
1500	500	20	0 (0–0)	0 (0–0)

bananas. The commodities contributed 17.0%, 15.2%, and 14.2% of the intake, respectively. When considering the upper tail of the distribution (>97.5%), soya-based drinks become the major contributor to the exposure (19.6% of the intake), followed by apple, banana, and bread and rolls. Because apples and bananas were not included in the UK monitoring of glyphosate, the optimistic assessment, which does not replace missing values, treats intakes for these commodities as true zeros. In contrast, the pessimistic assessment uses the MRL as a surrogate for gaps in the monitoring data, which is a conservative assumption. The optimistic and pessimistic assessments may therefore be treated as best- and worst-case outcomes, with the true exposure falling between the two results.

4. Discussion

In 1989, the World Health Organization published guidelines for predicting dietary exposure to pesticides; these were subsequently updated in 1997 following a joint FAO/WHO Consultation. The underlying principles of chronic dietary exposure assessment for pesticides have not changed fundamentally since the issue of this guideline. However, the establishment of the European Food Safety Authority (EFSA) in 2002 and the introduction of new European legislation have led to significant developments in terms of the tools and data available for dietary exposure assessment, including the Pesticide Residues Intake Model (PRIMo) for European dietary exposure assessment, which has been used for the theoretical maximum daily intake (TMDI) and national estimated daily intakes (NEDI) calculations presented above.

In 2004, Harris and Gaston used glyphosate as an example to demonstrate the impact of using stepwise, refined predictions of the chronic dietary exposure. Estimates were made using the UK CRD (Chemicals Regulation Directorate) chronic exposure model based on consumption patterns for the UK toddler and adult populations, considering the exposure from treated cereal crops. The assessment was refined taking into account the available processing factors derived from the EU review and consumption data for processed cereal products, rather than being expressed as the raw agricultural commodity (RAC; e.g., barley beer and wheat flour, rather than grain). Data from supervised residues trials, conducted to give rise to the highest likely residues according to a particular use pattern, were also refined by substitution with pesticide residues monitoring data from UK surveys (1999–2003). The refined assessment led to chronic intakes accounting for 0.6% of the acceptable daily intake (ADI; chronic dietary exposure end-point) compared to 11.1% of the ADI using the most conservative model (UK toddler intakes and STMR-p inputs). The current assessment updates that were made previously (Harris and Gaston, 2004) and considers the potential long-term exposure to glyphosate from the total diet and for the whole of Europe and globally.

The TMDI represents a worst-case exposure scenario, which can provide a first-tier screening assessment of the potential exposure to a substance. The estimate is based on the average daily consumption of food containing the highest likely residues (MRL). The Joint Meeting on Pesticide Residues (JMPR) acknowledges that this calculation can result in a gross overestimation of the true intake when all potential uses are considered (FAO, 2009). The TMDI makes a number of conservative assumptions, including that all crops have been treated and all contain residues at the highest probable levels, and that residues are present at the level of the default MRL, even in crops for which there are no authorised uses. In the current study, the glyphosate TMDI used the current EU MRLs as input values for the full range of foodstuffs, including animal origin products, as well as conversion factors to account for the proportion of metabolites not reflected by the MRL. The calculated TMDI was below 100% of the ADI for all European diets, with the UK toddler having the highest intakes at 80.1% of the ADI. The major contributor to the UK toddler diet was sugar beet (root), based on intakes at the MRL of 15 mg/kg. Because sugar beet is almost exclusively consumed after processing to refined sugar, use of the residue found in the raw commodity represents a substantial overestimation of the residue intake expected from the food as consumed. Processing information assessed by the JMPR in 2011 demonstrates that the process of refining sugar from beets leads to a reduction in residues by a factor of <0.01, and maximum residues of glyphosate in sugar are therefore expected to be below 0.15 mg/kg. Taking account of the loss of residues during processing decreases the exposure contribution from sugar beet from 68.6% to 0.7% of the ADI, and produces an overall adjusted TMDI of 12.2% of the ADI. Furthermore, based on conversion from the raw agricultural commodity (sugar beets) to the consumed product (sugar), the UK toddler diet is reported to include an average of 57 g sugar per day. This is based on a dietary survey conducted before 1995. A more recent UK survey, the 2008–2012 National Diet and Nutrition Survey (NDNS) rolling programme, reports sugar intakes for this age group at an average of 36 g per day, which would lead to further reductions in the exposure to glyphosate through sugar consumption.

It is noted that the EU and Codex definition of the residues for MRLs/enforcement is glyphosate alone, whereas the definition of the residue for risk assessment includes not only glyphosate but also AMPA, N-acetyl glyphosate, and N-acetyl AMPA, as applicable. These residues may be present in varying amounts in treated crops, depending on the use pattern and crop to which glyphosate has been applied. The EU review of glyphosate concluded that AMPA presents a similar toxicological profile to glyphosate and that the reference values (ADI) of the latter apply to AMPA (EFSA, 2015b). Previous assessments concluded that the N-acetyl metabolites are of no higher toxicity than glyphosate (EFSA, 2009a,b); therefore the ADI may also apply for these compounds. The discrepancy in the residue definitions for risk assessment and MRLs/enforcement means that conversion factors are required to be included in the TMDI, where these metabolites are expected to make a significant contribution to the exposure (EFSA, 2015b). Using the EU MRLs and conversion factors for tolerant crops and products of animal origin, the overall TMDI with no additional refinements accounts for 80.1% of the ADI for the UK toddler. By substituting the MRLs for the available STMR values (NEDI approach), taking into account the residue definition for risk assessment, the intakes for the UK toddler decrease to 16.8% of the ADI. The TMDI therefore provides a tool by which a simple screening assessment can be performed, but it does not give a realistic estimate of exposure due to its conservative nature.

The national estimated daily intake (NEDI) refines the assumptions of the TMDI by substituting the MRL value for the supervised trials median residue (STMR) to give a more realistic estimate of the level of residues to which the consumer may be exposed on a daily basis. The input values used for the NEDI are summarised in Table 2 and, where available, these are the STMR values arising from the critical use on which the EU MRL is based, and according to the residue definition for risk assessment. For some crops, the default EU MRL values have been used where there have been no recent assessments; it is therefore not clear whether a use exists that could lead to detectable residues being present below the default level. The STMR values used were abstracted from EU assessments in the public domain; the renewal assessment report (RAR, 2013), the draft assessment report (DAR, 1998) or EFSA reasoned opinions (as cited in Table 2). Additional STMR values were taken from JMPR assessments, generally where EU MRLs are based on uses in third countries that may be exported to the EU. The residues cover the appropriate definition for risk assessment, either by direct measurement or by application of conversion factors.

Whilst use of the available STMR data leads to a substantial reduction in the calculated intakes, the NEDI remains a conservative assessment intended to provide a high level of protection for the consumer. Supervised residue trials are conducted according to the critical use of a pesticide and are intended to give information on the highest likely residues that may result from such use (EC, 1997). The NEDI also makes the same conservative assumptions as the TMDI regarding the proportion of crops treated, and no account is taken of the potential loss of residues during food storage and preparation. Monitoring activities in the EU are co-ordinated by the European Commission and EFSA, and set out in the multi-annual control programme (EC, 2014b). The programme aims to include the major foodstuffs that make up the European diet, which are monitored over a 3-year period. Member States also report on their national control programmes, which are complimentary to the EU-coordinated programme. In the EFSA 2013 European Union Report of pesticide residues (EFSA, 2015a), the majority of pesticides found in the monitoring, including glyphosate, were concluded to present no long-term risk for consumers (0.51% ADI for glyphosate) based on a limited range of crops. EFSA noted that the risk assessment method used should be considered as a conservative screening and indicated that higher-tier calculations could be achieved by means of probabilistic modelling.

Because monitoring data give a more realistic—albeit retrospective—estimate of the residues to which consumers are exposed, mean residues detected in the EU programme, or the UK national monitoring activities, were substituted for STMR values in order to conduct a refined NEDI (Table 10). Where residues of glyphosate were low (<0.05 mg/kg), as for orchard fruit, vines, and vegetables, no conversion factor was applied, because the contribution of the AMPA metabolite is expected to be low. For the pulses and cereal crops, conversion factors were applied. The use pattern for citrus fruits is likely to be similar for all fruits within the group, and mandarins, being a small citrus, are likely to represent a worst-case in terms of residues; therefore, the mean residue for mandarins has been extrapolated to the whole citrus group. Overall, the available EU monitoring data for glyphosate is not comprehensive, because analysis of glyphosate residues is mandatory only for cereals in the EU. The availability of more comprehensive monitoring data, covering a wider range of crops, could potentially allow further significant refinements to the dietary exposure estimates.

Processing factors were also applied to the mean monitoring or STMR values where the commodity is typically consumed in a processed form (e.g., rapeseed oil). Using these refinements, the intake was estimated to account for 2.1% ADI, of which barley consumption was a major contributor. Further, consumption data for barley were available at a lower level of aggregation, which gave specific consumption values for barley consumed as breakfast cereals, beers and malt. Applying processing information to the barley STMR for these commodities allowed a further refinement, which reduced the total dietary exposure to 1.2% ADI. Using the same inputs with the German national dietary intake model resulted in intakes of a similar magnitude. Both the EU and German national assessments could be refined further if additional data on other domestic and industrial processes were available. Similar to the PRIMo critical diet (Irish adult), consumption of barley by the German adult is predominantly as beer (58%), and because the major contributor to the German adult diet is barley, a further refinement could be possible taking into account that glyphosate residues in beer are expected to be lower than in grain by a factor of 0.03. For foods that are not typically consumed raw, further reductions in residues could be anticipated following domestic cooking processes.

The WHO GEMS/Food 17 Cluster Diets IEDI model is used by the JMPR to estimate global intakes to a pesticide when making recommendations for establishing Codex MRLs (FAO/WHO, 2014). This model incorporates global dietary information, derived from FAO (Food and Agriculture Organization of the United Nations) food balance sheets and grouped into clusters depending on the estimated level of per capita consumption. The IEDI model based on the GEMS/Food cluster diets (WHO, 2012) provides more detailed information on the food as consumed compared to the EU models described above. This allows the direct use of monitoring data for processed or composite commodities and/or the application of a wider range of processing information, where available. Global intakes using this tool ranged from 0.33% to 0.97% of the ADI for the individual regional diets. The most exposed population was cluster C02, and as with the VELS model, the highest intakes of any individual commodity were for sunflower, based on the residue measured in the seed. Processing data for these commodities, or an appropriate surrogate, to address the expected reduction of residues during oil production, could further refine and decrease the estimated global intakes.

Probabilistic approaches combine dietary information and chemical occurrence data to estimate the distribution of intakes amongst individuals within a population, to achieve a more realistic estimate of exposure compared to deterministic approaches by incorporating uncertainty and variability into the assessment. In the EU, probabilistic methods have not been employed routinely for pesticide risk assessment. In contrast, in the US, probabilistic methods have played an increasingly important role in risk assessments conducted by the Environmental Protection Agency since the release of policy and guidance information in 1997 (USEPA, 1997a,b). Following the guidance of the EFSA PPR panel (EFSA PPR, 2012), a basic probabilistic assessment was performed according to the defined optimistic and pessimistic scenarios. The assessments were made on the basis of residues measured in the UK monitoring programme (PRiF, 2011, 2012, 2013, 2014). Further monitoring data for glyphosate are available from the EU co-ordinated monitoring programme, where glyphosate is a mandatory analyte in cereals; however, the level of detail in the EFSA reports is insufficient for input into the MCRA 8.0 tool, which requires the data to be presented at the sample level. As such, only the UK monitoring data have been used for this assessment. For the pessimistic scenario, because the monitoring data do not cover the full range of consumed commodities, the model selects the MRL values to complete the concentration database.

Both the monitoring data and the MRLs are based on the analysis of glyphosate without any contribution from the metabolites. Additional exposure data on the analysis of the metabolites and/or conversion factors for each of the commodities would be required to address this. However, due to the processed/composite nature of many of the commodities for which monitoring data are available, it was not possible to derive robust conversion factors. As noted for the NEDI calculations, the STMR values based on the risk assessment residue definition are lower than the MRL set on a parent-only basis, and in many cases, the metabolite contribution is zero. Conversion factors for lentils (dry) and cereal grains are in the range of 1.05–1.1 for the raw agricultural commodities, indicating that the metabolites would contribute very little in addition to the estimated exposure. Possibilities for additional refinement include the use of supervised trials residue data in place of MRLs and the use of measured values from feeding studies to refine the contribution from commodities of animal origin. Taking these uncertainties into account, the pessimistic scenario can still be considered to give a conservative upper estimate of the realistic exposure. For the adult assessment, no person-days were found to exceed 1% of the ADI, whereas for the child, intakes were predicted to be higher, with approximately 115 person-days per million expected to exceed 1% of the ADI. The P99.9 intake for the Dutch child was 4.49 μg/kg bw/day (3.80–4.85 confidence intervals; 0.9% of the ADI). This intake is lower than any of the deterministic assessments made, despite assuming that all produce was treated and contained residues at the monitoring or MRL level, even where there is no authorised use on a given crop. Furthermore, the pessimistic assessment assumed that all residues reported as being below the reporting limit of the analytical method (LOR) were in fact present at that level. Despite the conservative assumptions made in the pessimistic model run, the outcome from the probabilistic assessment, estimating a lower exposure compared to the refined deterministic approach, is not unexpected. It is noted in the EFSA Guidance on the use of probabilistic methodology that these approaches should be complementary to, but not replacements for deterministic approaches. Probabilistic approaches achieve a more realistic exposure by using distributions to represent the range of variation within the datasets for consumption and residue concentration (EFSA PPR, 2012). In contrast deterministic assessments use conservative point estimates for these parameters taken from the upper end of the distribution of values. Despite the limitations in the data available to make this assessment, the indicative results demonstrate what an important tool the probabilistic method can be for conducting realistic dietary exposure estimates.

5. Conclusions

Overall, the TMDI can be useful as a screening tool to rapidly identify potential risks to the consumer, but it can be demonstrated that it overestimates actual exposure and does not give a realistic estimate of dietary exposure. By systematic use of refinements, such as substituting MRLs for median residue levels and the use of processing and residues monitoring information, the total modelled exposure to glyphosate is reduced by a factor of 67. This estimate could be refined further by additional monitoring or processing data, or using refined modelling based on the probabilistic method developed by the EFSA Panel on Plant Protection Products and their Residues (EFSA PPR, 2012). The refined chronic dietary intake of glyphosate for the critical EU diet (Irish adult), using the deterministic approaches employed in PRIMo rev. 2, was 0.0061 mg/kg bw/day, or 1.2% of the ADI of 0.5 mg/kg bw/day. The exposure level at which no adverse effect was seen (i.e., the no-observed-adverse-effect level, or NOAEL), in the studies used to derive the ADI, was approximately 8200 times higher than this refined chronic dietary intake. Indicative probabilistic calculations, based on the EFSA PPR guidance, show that the actual chronic dietary exposure is likely to be even lower (<0.0045 mg/kg bw/day; P99.9). In 2004, the JMPR established an ADI of 1 mg/kg bw/day (WHO/FAO, 2004), and in 2006, the US EPA set a chronic population-adjusted dose (cPAD) of 1.75 mg/kg. Since the EU ADI has been used in these risk assessments, it represents the most conservative assumptions regarding the endpoint, globally.

Declaration of interests

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