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Exploring the half-life of glyphosate in human urine samples

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ABSTRACT

Background: The International Agency for Research on Cancer (IARC) has recently classified glyphosate as a Group 2A ‘probably carcinogenic to humans’. Due to this carcinogenic classification and resulting international debate, there is an increased demand for studies evaluating human health effects from glyphosate exposures. There is currently limited information on human exposures to glyphosate and a paucity of data regarding glyphosate’s biological half-life in humans.

Objective: This study aims to estimate the human half-life of glyphosate from human urine samples collected from amenity horticulture workers using glyphosate based pesticide products.

Methods: Full void urine spot samples were collected over a period of approximately 24 h for eight work tasks involving seven workers. The elimination time and estimation of the half-life of glyphosate using three different measurement metrics: the unadjusted glyphosate concentrations, creatinine corrected concentrations and by using Urinary Excretion Rates (UER) ($\mu\text{g L}^{-1}$, $\mu\text{mol/mol}$ creatinine and $\text{UER } \mu\text{g L}^{-1}$) was calculated by summary and linear interpolation using regression analysis.

Results: This study estimates the human biological half-life of glyphosate as approximately 5 ½, 10 and 7 ¼ hours for unadjusted samples, creatinine corrected concentrations and by using UER ($\mu\text{g L}^{-1}$, $\mu\text{mol/mol}$ creatinine, $\text{UER } \mu\text{g L}^{-1}$), respectively. The approximated glyphosate half-life calculations seem to have less variability when using the UER compared to the other measuring metrics.

Conclusion: This study provides new information on the elimination rate of glyphosate and an approximate biological half-life range for humans. This information can help optimise the design of sampling strategies, as well as assisting in the interpretation of results for human biomonitoring studies involving this active ingredient. The data could also contribute to the development or refinement of Physiologically Based Pharmacokinetic (PBPK) models for glyphosate.

1. Introduction

Glyphosate is a broad spectrum, post emerging, organophosphate herbicide and is currently the highest volume herbicide used globally (Benbrook, 2016; Guyton et al., 2014). Recently, glyphosate has come under international debate since the International Agency for Research on Cancer (IARC) classified the chemical as a ‘Group 2A – probably carcinogenic to humans’ (IARC, 2016). However, a number of European and international agencies, as well as international experts, have classed glyphosate as non-carcinogenic to humans (ECHA, 2017; EFSA, 2017; JMPR, 2016; US EPA, 2016). Many reasons are presented for the divergence of opinion between the outcome of the IARC evaluation and

the EU assessment of glyphosate. These include the use of different data sets and different methodological approaches on how toxicity data was weighted and assessed. For example, new toxicological data on the carcinogenicity of glyphosate in animals was included in the EU assessment but not considered by IARC. While the IARC evaluation included scientific evidence on associations between exposure and development of non-Hodgkin lymphoma in humans, this was considered weak and insufficient for classification in the EU assessment process (Tarazona et al., 2017). In 2017, the European Commission authorised the use of glyphosate for a further 5 years (European Commission, 2018).

Despite the extensive use of glyphosate based pesticide products and

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concerns over the potential adverse health effects associated with its use (Myers et al., 2016), there is limited human exposure data for glyphosate in occupational (Acquavella et al., 2004; Connolly et al., 2017, 2018a; Curwin et al., 2007; Johnson et al., 2005; Mesnage et al., 2012) and environmental settings (Connolly et al., 2018b; Conrad et al., 2017; Mills et al., 2017; Parvez et al., 2018).

Biomonitoring, which involves the measurement of a chemical or relevant biomarkers in biological substances such as blood, urine, hair or milk, is considered the gold standard for exposure assessment (Sexton et al., 2004) and is common for pesticide exposure assessments (Aprea, 2012; Fustinoni et al., 2008). When developing a biomonitoring method, specific chemical and toxicological information is required to ensure accurate data generation and interpretation. When designing a suitable biomonitoring sampling strategy, it is necessary to consider the chemical toxicokinetics, metabolic variation between subjects (intraspecies variation) and the type of biomonitoring matrix to be used (e.g. blood, urine) (Barr et al., 2006).

Human biological half-life information and excretion patterns is especially important when designing urine spot sampling strategies (Barr et al., 1999), which are regularly used in pesticide exposure studies. Information on a chemical's excretion pattern guides when urine samples should be collected, allowing a more accurate interpretation of the exposure level.

Biomonitoring studies using urine samples have an additional complexity, as urine volume is not constant for each void. Short-term volume and excretion rates can vary substantially between voids, which can cause variability in chemical concentrations in spot urine samples. A suitable urine sampling collection strategy is critical for occupational exposures, especially for non-persistent pesticides (pesticides with a short half-life), as any variation in the timing of sample collection after exposure can result in variations in exposure estimates.

Sampling methodologies to normalise spot urine samples and account for the fluctuations in the volume of the void remains an area of continual research (Barr et al., 2005). To correct for the variations in the volume between voids, results from biomonitoring studies can be expressed by adjusting for specific gravity (i.e. ratio between the density of urine and pure water at a constant temperature (Chadha et al., 2001)) or for creatinine, by calculating the urinary excretion rate or by just expressing results as mass over volume.

Adjusting for specific gravity is considered a more robust method for accounting for urine concentration volume variation (Haddow et al., 1994). However, disproportionate increases in specific gravity measurements can occur for people with strict dietary restrictions (e.g. vegetarianism, salt and/or protein restrictions), which requires a correction factor (Chadha et al., 2001; Pearson et al., 2008). Specific gravity analysis is not easily automated, thus, not widely employed.

Creatinine, a creatine metabolite, is a normal endogenous end product in the human body that is excreted at a relatively constant rate and is inversely proportional to urine flow rate (Boeniger et al., 1993). These attributes make it a useful parameter for normalising results to account for fluctuations in urine volumes (Aprea et al., 2002). Creatinine corrections can reduce uncertainty due to urine volume variability but many factors can cause fluctuations in creatinine levels including age, gender, diet, physical activity or underlying diseases (e.g. diabetes) (Boeniger et al., 1993). Moreover, morning void samples have potentially higher creatinine levels than urine samples taken at other times during the day (Barr et al., 2005). There is also the potential for large variability of creatinine excretion between short-term voids (< 4 hours (h)) (Boeniger et al., 1993) and it is advised to exclude samples with creatinine levels less than 3 mmol L^{-1} or greater than 30 mmol L^{-1} as they can cause inappropriate interpretation of the results (Cocker et al., 2011; EWDTS, 2002). Despite these limitations, it is a widely used and reported metric.

Variation in urinary concentrations due to urine volume fluctuations can be reduced by using Urinary Excretion Rates (UER), which involves the calculation of the chemical concentration in each void,

corrected for the time period between voids (Rigas et al., 2001). A disadvantage of using this method is that the collection of many samples is expensive and can be a logistically impractical study to conduct.

Glyphosate is largely not metabolized in the human body and thus the parent compound can be measured in urine. Extrapolations from animal toxicological studies (oral ingestion of glyphosate in rats) suggested an elimination half-life of 33 h for glyphosate for humans (IARC, 2016). Another animal study suggests a first phase half-life at 6 h (Williams et al., 2000). However, animal toxicological tests do not always translate to the human metabolism (Barr et al., 1999). A recent human study involving two participants, that ingested an oral dose of glyphosate, equivalent to 25% of the European Food Safety Authority's (EFSA) Acceptable Daily Intake (ADI) allowance, suggests a rapid phase half-life between 4 and 17 h (Faniband et al., 2017). There is currently inconsistent information on the human biological half-life and excretion rates for glyphosate. More reliable and accurate information would assist in the development of, for example, exposure assessment sampling protocols, interpretation of biomonitoring results and development and refinement of Physiologically Based Pharmacokinetic (PBPK) models.

The current study involved the collection of multiple spot urine samples over a 24 h period as part of a biomonitoring occupational exposure assessment study for glyphosate. Samples were collected from seven workers performing eight tasks involving applying glyphosate based pesticide products. The data was analysed to investigate the elimination rate of glyphosate from the human body. Full void urine samples were collected and analysed for creatinine, alongside glyphosate. Elimination rates were calculated using three differing measuring metrics, the unadjusted glyphosate concentrations, creatinine corrected concentrations and by using Urinary Excretion Rates (UER) ($\mu\text{g L}^{-1}$, $\mu\text{mol/mol creatinine}$ and $\text{UER } \mu\text{g L}^{-1}$), to ascertain whether there was a substantial difference when volume correction factors were used for urine samples. The aim of the current study, which to the authors' knowledge is the first published peer review article of its kind, was to approximate the potential half-life time range of glyphosate from human urine samples.

2. Materials and methods

2.1. Site description and study population

An occupational urinary biomonitoring study for glyphosate was carried out from September 2016 to September 2017. Sample collection took place at the Irish Commissioner for Public Works (OPW) field sites, the Irish governing body with responsibility for the maintenance of the State's property portfolio including the national parks and historic monuments (OPW, 2018). Further details and results from the occupational exposure study involving the collection of individual spot urine samples has been previously published (Connolly et al., 2018a).

In brief, tasks completed by the workers sampled were classified into three similar exposure groups (SEGs), based on the application method used by the workers to apply glyphosate based pesticide products. Workers used manual knapsacks, pressurised applicators and controlled droplet applicators, all of which involved the use of a handheld lance. The manual knapsack, typically a 10 or 15 L container with a manual lever, was carried on the users back. The pressurised lance was connected to a motorised/pressurised knapsack, operated at 2–6 bar pressure. The controlled droplet applicator involves users carrying a small lightweight container containing a pre-mixed pesticide solution. This applicator nozzle has an adjustment for the droplet size, which can increase the droplet size to reduce drift.

Ethics approval for the biomonitoring study was obtained from the National University of Ireland, Galway's Research Ethics Committee (Ref: 16-July-19) on the 5th September 2016. Participation in the study was voluntary and informed consent was received from all participants. Contextual information for the study was collected via a self-

administered questionnaire (e.g. personal details, use of pesticides outside of work and dietary habits) and researcher observations of the pesticide application task were recorded in an activity diary.

3. Biological monitoring

3.1. Urine collection

The biomonitoring study adopted a convenience sampling approach, where participants completed tasks involving glyphosate based pesticide products that were part of their normal work duties. The researcher was on site during sampling to observe and collect contextual information to support all of the work tasks (Connolly et al., 2018a).

Full void urinary spot samples were collected from the participants using 1 or 2 L pre-labelled containers for 29 work tasks, which were collected and analysed separately for glyphosate. A minimum of three urine samples were collected from each participant: one sample before the task began (pre-task sample), one sample taken within an hour of completing the work task (post-task sample) and the first morning void sample obtained the day after completing the work task (following first morning void).

Participants had an option to provide individual spot urine samples for all urinary voids from the start of the pesticide task to the following first morning void. A pre-labelled sample container was given to every participant for each void and they were asked to write the time and date on the container label. To reduce the potential of sample contamination, participants were provided with written instructions on the correct hand-washing procedure to complete before giving a sample.

The researcher collected the pre- and post-work task samples during the exposure assessment period (while on-site) and returned the following morning to collect the following first morning void and all additional samples provided. The sample volume of each urine sample provided was recorded and an agitated 20 ml aliquot of each was transferred into a Sterilin™ pot, labelled with a unique identifier number, date and time. The researcher used disposable nitrile gloves when handling all samples and changed them between handling samples. All samples were frozen to -18°C within 24 h of collection, until laboratory analysis. All equipment used was triple rinsed with water, with equipment and work surfaces being cleaned with a biological disinfectant before and after handling urine samples.

3.2. Urine sample analysis

Chemical analysis was completed by the Health and Safety Laboratory (HSL), Buxton, UK. All samples were prepared and analysed for glyphosate following analytical methods previously described in Connolly et al. (2017), with minor alterations. In brief, glyphosate was extracted from urine samples (200 μl diluted with 800 μl deionised water) using strong anion exchange solid phase extraction (SPE) eluted with 10% formic acid in methanol. Quantitative analysis was performed by liquid chromatography tandem mass spectrometry (LC-MS/MS). Chromatographic separation was achieved on a Zorbax XDB-C8, 150×4.6 mm, 5 μm (Agilent, Stockport, UK) column with mobile phases of 0.1% formic acid and acetonitrile with a gradient elution. The analytical method was linear over the range 0–20 $\mu\text{g L}^{-1}$ and intra and inter assay coefficient of variations (CVs) of 3.54% ($n = 10$) and 9.96% ($n = 40$, over 4 runs) were achieved. The analytical limit of quantification (LOQ) was 0.5 $\mu\text{g L}^{-1}$. Creatinine analysis was also completed on all urine samples using an automated alkaline picrate method using a Pentra 400 clinical analyzer (Cocker et al., 2011).

3.3. Data analysis

Of the 29 exposure assessment tasks evaluated in this study (Connolly et al., 2018a), 17 (59%) had greater than three individual spot urine samples collected over the exposure assessment period (from

pre-work task to the following first morning void). To explore the elimination rate and to estimate the potential human biological half-life of glyphosate, only work tasks with at least two spot urine samples collected after the peak exposure were included for excretion profile analysis. The peak urinary exposure value was defined as the highest urinary glyphosate concentration detected in spot sample after the pesticide application, over the exposure assessment period, per task.

Chemical analysis included the measurement of creatinine and results were expressed as glyphosate unadjusted values in microgram per litre ($\mu\text{g L}^{-1}$) and in micromole of glyphosate per mole of creatinine ($\mu\text{mol/mol creatinine}$). The volume of each spot urine sample was also recorded and this allowed for the results to also be corrected for the volume of the void by using Urinary Excretion Rates (UERs) (Rigas et al., 2001)(Eq. (1)). The UER ($\mu\text{g L}^{-1}$) was calculated by taking the glyphosate concentration (C_U) of the spot urine sample and multiplying it by the volume of the void (V_U) and then dividing this by the duration of time the void accumulated in the bladder ($T_C - T_T$), which is the urine sample collection time (T_C) minus the time from the last urination (T_T).

$$UER = \frac{C_U V_U}{(T_C - T_T)} \quad (1)$$

3.4. Statistical analysis

All statistical analysis were performed on Microsoft Excel and Stata Software (StataCorp., 2015). Glyphosate concentrations were log-transformed as the data showed a log normal distribution. The period of peak sample collection (highest glyphosate concentration sample within the measured period) was taken as the start time ($t = 0$). The time period from the sample collection time ($t = 0$) to each preceding sample was calculated. The slope of the glyphosate urine concentration by the time duration (time passed from the start time) was calculated for each task. Linear interpolation using regression analysis were also performed for each of the included tasks. Data analysis was completed using three measurement metrics: a) the unadjusted concentrations, b) creatinine corrected concentrations and c) using the UER corrected values.

The mean values, as well as the 95% confidence interval of the half-lives were calculated to estimate the half-life range for each measurement metric.

4. Results

Urine samples from seven participants performing eight work tasks involving glyphosate based products were analysed. Data from six males and one female worker is included in this study; one male participated twice on two consecutive days. The age range was from 32 to 60 years, with an arithmetic mean (AM) of 48 years. Workers carried out work tasks that involved the application of glyphosate based pesticide products within one of the SEGs, which lasted between approximately 1–6 h daily. The total sampling time duration of the selected eight work tasks included in the data analysis, ranged from approximately 19–26 h.

In total, 28 individual spot urine samples were analysed for the eight work tasks included in this study (three to four spot urine samples per sample set). Each sample set was analysed to evaluate the relationships between the measured urinary glyphosate concentrations ($\mu\text{g L}^{-1}$, $\mu\text{mol/mol creatinine}$ or UER) and the duration. The duration started from the peak concentration sample (start time) to each of the subsequent samples. Correlations and linear regression analysis was performed for each sample set, with an example for one sample set shown in Fig. 1 and the remaining sample sets are shown in supplementary information.

Four sample sets were excluded from the analysis: two creatinine corrected samples sets ($\mu\text{mol/mol creatinine}$) and two UER calculated

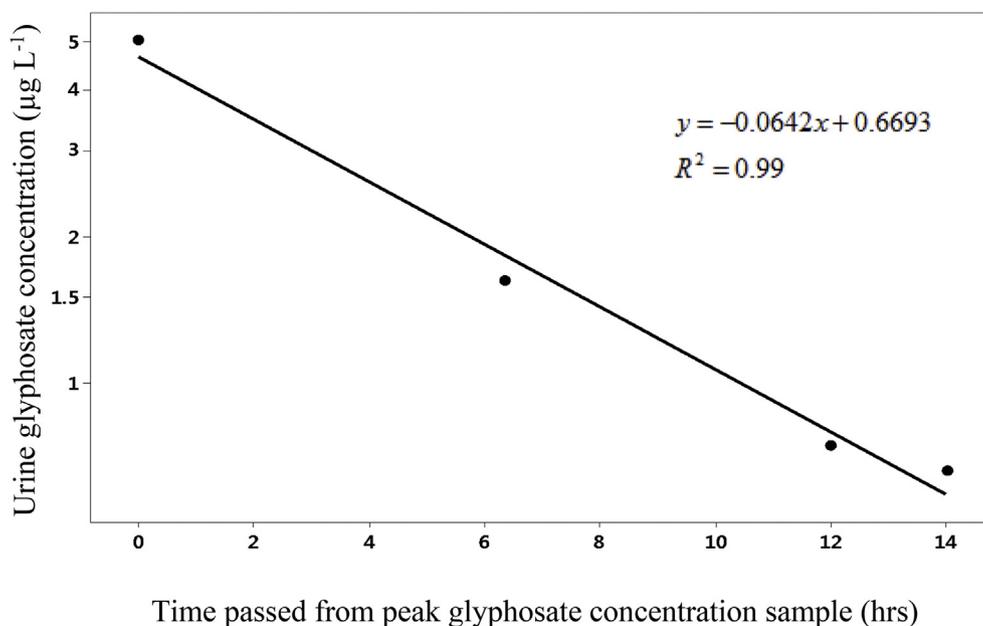


Fig. 1. Sample set number 2, showing the decline in glyphosate concentration ($\mu\text{g L}^{-1}$) in the urine samples ($n = 4$), over the time period (0–14 h), from the peak glyphosate concentration sample. The linear regression analysis is shown on the graph.

sample sets. One creatinine corrected sample set was excluded due to low creatinine levels ($< 3 \text{ mmol/L}$) in individual spot urine samples and another because there was no association between concentrations and duration of sampling. This lack of association could relate to a number of factors like gender, diet and hydration (Boeniger et al., 1993). Two UER calculated sample sets were excluded from analysis, as the sample sets no longer had two spot urine samples following the peak exposure when UER was corrected.

Each of the sample sets showed a moderate to strong relationship between concentration and duration for all samples ($R^2 = 0.42\text{--}1.00$), with an estimated half-life ranging approximately from $1 \frac{1}{2} - 10 \text{ h}$ for unadjusted values ($\mu\text{g L}^{-1}$) or between $4 \frac{3}{4} - 20 \text{ h}$ for creatinine corrected values ($\mu\text{mol/mol creatinine}$). When the results were restricted to sample sets which showed a very strong relationships ($R^2 > 0.90$), the estimated half-life average (range) was $4 \frac{1}{2} (1 \frac{1}{2} - 7)$ hours and $7 \frac{1}{2} (4 \frac{3}{4} - 9 \frac{1}{4})$ hours for unadjusted and creatinine corrected values, respectively.

UER calculated samples showed moderate to strong relationship ($R^2 = 0.60\text{--}0.95$), with an estimated half-life average (range) of $7 \frac{1}{4} (3$

and $9 \frac{1}{2})$ hours (UER $\mu\text{g L}^{-1}$). The average glyphosate half-life including all measuring metrics was approximately $5 \frac{1}{2}$ to 10 h (Table 1).

The average and range of the half-life on sample sets (number 2, 12, 19 & 30) that had all three measuring metrics included was calculated. Sensitivity analysis on the four sample sets, common across all measuring metrics, had an estimated half-life average (range) of approximately $6 \frac{1}{2} (4\text{--}10)$, $11 \frac{3}{4} (7 \frac{1}{4} - 20)$, and $6 \frac{1}{2} (3\text{--}7 \frac{3}{4})$ hours for the unadjusted glyphosate concentrations, creatinine corrected concentrations and by using UER ($\mu\text{g L}^{-1}$, $\mu\text{mol/mol creatinine}$ and UER $\mu\text{g L}^{-1}$), respectively.

5. Discussion

To the authors' knowledge, this study is the first published peer reviewed article estimating the biological half-life of glyphosate using human urine samples. Analysis of glyphosate concentrations using three measuring metrics (unadjusted concentrations, creatinine corrected concentrations and UER calculated concentrations) suggests a human biological half-life between approximately $3 \frac{1}{2}$ and $14 \frac{1}{2}$ hours (95%

Table 1

Results from linear regression analysis examining the half-life of glyphosate using human biomonitoring samples. Analysis is performed with urine glyphosate concentrations, samples adjusted for creatinine and adjusted for volume ($\mu\text{g L}^{-1}$, $\mu\text{mol/mol creatinine}$ and adjusted for urine volume in $\mu\text{g L}^{-1}$, respectively) as the dependent variable and time period (in hours) elapsed from the peak concentration sample as the independent variable.

Sample set number	Glyphosate $\mu\text{g L}^{-1}$				Glyphosate $\mu\text{mol/mol creatinine}$				Glyphosate $\mu\text{g L}^{-1}$ (UER)			
	N*	Slope	R ²	Half-life (hrs)	N*	Slope	R ²	Half-life (hrs)	N*	Slope	R ²	Half-life (hrs)
2	4	0.06	0.99	4.69	3	0.04	1.00	7.31	3	0.04	0.88	6.94
13	4	0.04	0.99	7.06	4	0.03	0.98	9.25	4	0.04	0.89	7.84
14 ^a	3	0.19	0.99	1.61	3	0.06	1.00	4.77				
16 ^a	3	0.08	0.98	3.57					3	0.04	0.60	8.49
19	3	0.03	0.88	10.06	3	0.01	0.81	20.15	3	0.04	0.86	7.57
26	3	0.05	0.97	5.71	3	0.04	0.98	8.43				
28	4	0.04	0.42	7.40					3	0.03	0.62	9.51
30	3	0.08	0.96	3.99	4	0.03	0.76	10.08	3	0.10	0.95	3.16
	Mean Half-life (hrs)			5.51	Mean Half-life (hrs)			10.00	Mean Half-life (hrs)			7.25
	95% Confidence Interval			3.56–7.46	95% Confidence Interval			5.47–14.53	95% Confidence Interval			5.38–9.12

*UER = Urinary excretion rate; N = number of urine samples; R² = coefficient of determination as estimated by linear regression analysis. Sample sets that no longer had a sufficient number of samples after the peak concentration sample when adjusted for volume (glyphosate $\mu\text{g L}^{-1}$ (adjusted for volume)), sample sets with low creatinine levels (glyphosate $\mu\text{mol/mol creatinine}$) and sample sets with a weak association have been excluded from the analysis. ^a Participant who completed two separate work tasks in this study.

confidence interval).

Sensitivity analysis results did not alter the main conclusions of the study; however, the observed differences between unadjusted glyphosate concentrations and using UER concentrations narrowed. Irrespective of the measurement metric used, the time range is considerably lower than the half-life estimates reported in the IARC monographs (IARC, 2016) but are within the range of the half-life estimates reported in a previous human volunteer study (Faniband et al., 2017). The human volunteer only involved two subjects and the results varied substantially between both subjects. The study only evaluated the ingestion route of exposure (Faniband et al., 2017). Results from occupational pesticide exposure studies suggest that the dermal exposure route is important, accounting for up to 99% of exposures (Aprea et al., 2004; Flack et al., 2008; Tuomainen et al., 2002; Vitali et al., 2009). However, comparable exposure estimates between the current study and the human volunteer study may suggest the role of inhalation or ingestion routes. Dermal absorption of pesticides can be delayed as the skin surface can act as a dermal reservoir (Griffin et al., 2000). Although elimination kinetics from different uptake routes should be comparable, it is important to also consider the absorption kinetics and the comparison of results should be done with caution.

Human biological half-life estimates, using UER calculations, ranged from approximately 5 ½ to 9 h (95% confidence interval), with an average half-life of 7 ¼ hours. Half-life estimates, using unadjusted and creatinine adjusted methods appear to be more variable than when UER calculations. Using the UER calculations as reported in (Rigas et al., 2001), may be a good method to normalise results and reduce difficulties associated with urine volume fluctuations for biomonitoring studies. There is, of course, a logistical issue with the sample collection strategy needed for UER calculations, as calculations can only be conducted if each full void urine sample is collected over the sampling period. To the best of our knowledge, the samples collected for this analysis involved the collection of all voids. Missing or incomplete voids will cause UER calculations to be unsuitable. In addition, such a strategy is costly and the collection of all individual full void spot urine samples in a study places a high burden on participants, which can result in non-compliance or research fatigue (Scher et al., 2006), such factors can lead to this sampling strategy being impractical.

The current study does have some limitations. Our study was somewhat limited by the convenient sampling approach adopted, which prevented standardisation of our methods such as the type of pesticide products used (with differing concentrations of the active ingredient within products) and quantity of pesticide used for the task, as well as the application methods and sampling times differing across the work tasks. A small sample size prevented the use of more elaborate statistical tests to identify differences due to sex or age. In addition, some of these workers perform pesticide application tasks on a daily basis and there is a possibility of delayed dermal absorption due to the skin reservoir effect from tasks performed the day before sampling. The results reported are for first order kinetics but there is a possibility that this may be followed by biphasic or multi-phasic kinetics, which may not be identified as urine samples were only collected over a time period of approximately 19–26 h. However, the present study does provide information that may help inform the design of biomonitoring sampling strategies and assist in the interpretation of results for glyphosate focused studies. The information on the elimination rate and estimated half-life could also be useful for the development and refinement of Physiologically Based Pharmacokinetic (PBPK) models for this widely used active ingredient. Recently, glyphosate was set as a priority substance for the Human Biomonitoring for the European Union initiative (HBM4EU) and this information could also be useful in the development of a HBM4EU work programme for glyphosate (HBM4EU, 2018).

6. Conclusions

The results from this study provides new information on the elimination rate and estimated human biological half-life of glyphosate using measurements from urine samples collected during an exposure assessment study. The human half-life of glyphosate, approximated in this study, was substantially lower than that reported in the IARC monograph.

The biological half-life information is useful information for exposure assessment studies. The timing of sample collection can be important for the correct estimation of exposure, especially for occupational exposure studies adopting spot sampling strategies for non-persistent pesticides (short biological half-life). Human half-life information is also required for an appropriate interpretation of urine biomonitoring results and for the development or refinement of PBPK models.

Glyphosate, which is a priority substance for HBM4EU and considering the international debate over its carcinogenicity, will require further exposure studies. The information reported in the current study will be useful for these future glyphosate exposure assessment studies, as well as in the development of a HBM4EU work programme for glyphosate itself.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijheh.2018.09.004>.

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