Evaluation of the impact of glyphosate residues in food on human health

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For estimating the potential impact of pesticide residue intake on human health, two parameters have to be taken into consideration :

- The actual level of pesticide residues in the diet (dietary exposure)
- The acceptable daily intake of the pesticide (based on toxicological properties of the compound)

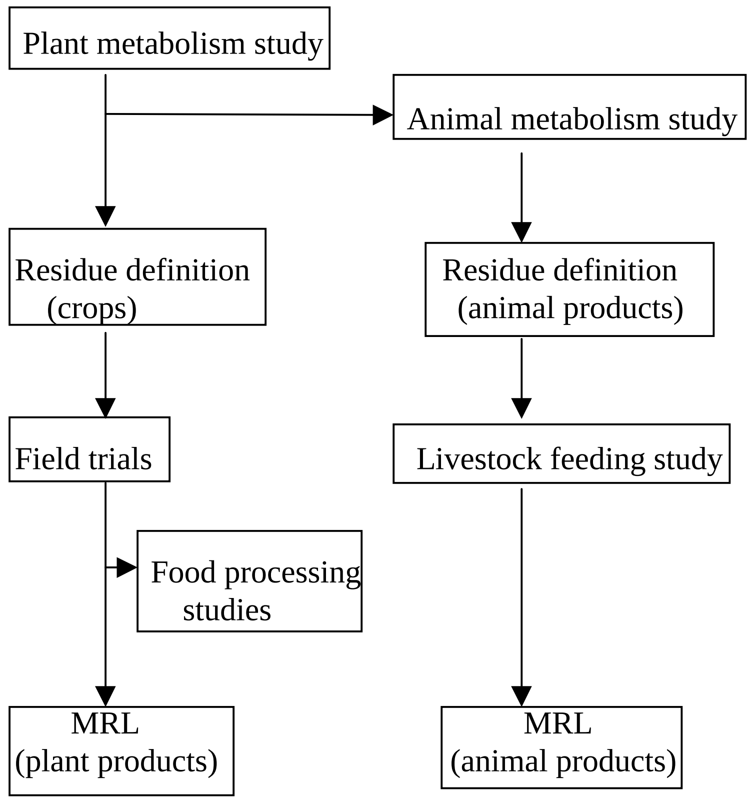
1. Determination of the level of pesticide residues in the diet

To predict the pesticide residue intake, information is required on :

- The amount of pesticide present in the food
- Average daily food consumption data

1.1. Pesticide residues in food

To determine pesticide residues in food, a series of studies have to be conducted in accordance with the requirements of the 91/414 EU guideline for pesticide registration. A schematic overview of the required studies is given below.



The ***plant metabolism study*** provides an estimate of the residue distribution (parent compound and metabolites) in the relevant parts of the crop, with particular emphasis on the edible parts of the crop (for humans and animals).
Based on the results of this study, a ***residue definition*** comprised of parent compound and/or relevant metabolites, as appropriate, is proposed for crops. The compounds listed in this residue definition will be analysed in the crops obtained from ***supervised field residue*** *studies* (minimum 16 for a use across Europe). The objective of these trials is:

- To quantify the highest likely residue level in treated crops at harvest following the proposed good agricultural practice
- To determine a median residue level in treated crops at harvest following the proposed good agricultural practice
- To determine, when appropriate, the rate of decline of plant protection product deposits

The results of the residue analyses of the crops obtained from the field trials will be used to propose a ***maximum residue limit (MRL)*** for a given use on a given crop. For a new use/new crop, field residue studies will have to be generated to calculate the MRL for this specific crop/use. The results will also be used to determine a median residue level for a given crop, referred to as the ***supervised trials median residue (STMR),*** which provides a more realistic estimate of consumer's expected exposure to residues. Since many plant products are processed before they reach the consumer, ***processing studies*** are performed to further allow a better estimate of consumer's exposure to residues.

The ***animal metabolism*** study provides information on the identity of the major components of the residues which may occur in the edible tissues (meat, milk, eggs) of livestock (typically lactating cows and laying hens) exposed to the compound and any relevant metabolites.
Based on the results of this study, a ***residue definition*** is proposed for edible tissues. The ***livestock feeding studies*** provide data on the quantitative transfer of residues to meat, milk, eggs and edible offal. Based on the results of these studies, a ***maximum residue limit (MRL)*** is proposed for the different foods of animal origin.

1.2.Food consumption data

Food consumption patterns vary considerably from country to country and even within a country. For predicting pesticide residue intake at international level, average food consumption estimates are based on Food Balance Sheet (FBS) data compiled by the Food and Agricultural Organization of the United Nations (FAO) Although food consumption data derived from such food balance sheets are subject to many uncertainties and limitations, they represent the best available source of data for international comparison and are adequate for predicting pesticide residue intake. The GEMS/Food Regional Diets are derived from the FAO FBS from selected countries and expert knowledge. Five regional diets are represented, namely Middle Eastern, Far Eastern, African, Latin American and European. Intake values (g/person/day) from the European diet have been used in this evaluation. Detailed consumption values can be found on the web site : http://www.who.int/fsf/GEMS/index.ht

1.3. Dietary exposure

The ***theoretical maximum daily intake (TMDI – mg/kg bw/day))*** of a given compound through diet can be calculated as follows:

$$TMDI = \frac{\Sigma F_i \times MRL_i}{bw}$$

Fi = intake of a given food commodity (kg/person/day)
MRLi = maximum residue level corresponding to that food commodity (mg/kg)
bw = body weight (60kg usually chosen)

This TMDI figure largely overestimates the exposure, as it assumes that all the consumed food is treated and contains residues at the MRL level.

The ***estimated daily intake (EDI – mg/kg bw/day)*** provides an estimate of expected dietary exposure and is calculated as follows:

$$EDI = \frac{\Sigma F_i \times STMR}{bw}$$

Fi = intake of a given food commodity (kg/person/day)
STMRi = standard trial median residue corresponding to that food commodity (mg/kg)
bw = body weight (60kg usually chosen)

The EDI figure provides a more realistic yet still conservative estimate of exposure, as it assumes that all the consumed food is treated, but that it contains a median rather than maximum level of residues.

2. Acceptable daily intake

The ***acceptable daily intake (ADI – mg/kg bw/day)*** for a given compound is derived from the toxicological database. The ADI is based on the lowest no effect concentration of the most sensitive species from a range of sub-chronic/chronic studies, to which appropriate safety factors are applied (10 for interspecies extrapolation, 10 for difference in sensitivity within a population, …).

3. Risk assessment

For estimating the impact of pesticide intake on human health, the theoretical maximum daily intake (TMDI) has to be compared with the acceptable daily intake (ADI), and is usually expressed as a percentage of the ADI.

$$\% = \frac{TMDI * 100}{ADI}$$

Given the overestimation of the presence of pesticide residues by the TMDI calculations, and the safety margins incorporated into the ADI, the use of PPPS is considered to be safe for human health if the TMDI is below the ADI.

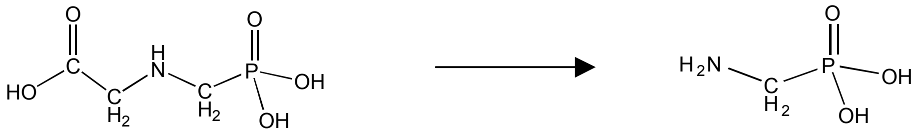
4. Studies performed with glyphosate

4.1. Crop metabolism study

The metabolism of glyphosate has been investigated in over 23 varieties of non-tolerant plants using different routes of uptake of glyphosate, including uptake from roots following application to the soil, direct application to foliage and stems, or direct uptake through the roots from a hydroponic solution, in order to define all potential routes of metabolism of glyphosate in crops. These metabolism studies supported the uses of glyphosate in non-tolerant crops, which include pre-emergent, pre-harvest and post-harvest treatments, plus some directed or selective applications, which generally result in only minimal contact of glyphosate with the crop during the main growth stages of the crop.

Following the development of crops tolerant to glyphosate, additional metabolism studies were conducted using in-crop applications of glyphosate to soyabeans, oilseed rape, maize, cotton, sugar beet and wheat tolerant to glyphosate, to define the metabolism in plants exposed to higher levels of glyphosate throughout the growing season.

The metabolic pathway of glyphosate in both non-tolerant and tolerant plants can be summarized as shown in the figure below: Glyphosate is metabolized to aminomethylphosphonic acid (AMPA) which is the main metabolite found in plants. AMPA can further react with naturally occurring organic compounds, or degrade to single carbon fragments that are incorporated into natural plant metabolic processes. The pathway is the same in non-tolerant and tolerant crops. The nature of the metabolites is the same, only the relative distribution varies depending on the speed and extent with which glyphosate is converted to AMPA.



Glyphosate AMPA

Minor metabolites

Degradation to single carbon fragments

Incorporation into natural products

4.2. Field residue studies

Numerous field residue trials were conducted on a variety of crops to document the various current Good Agricultural Practices of glyphosate in non-tolerant crops and potential future uses in tolerant crops in the northern and southern European regions. Samples taken at harvest were analysed for glyphosate and AMPA content to determine MRL and STMR levels.

Preemergent applications of glyphosate typically produce nondetectable levels of glyphosate in crop commodities, and result in MRLs of 0.1 mg/kg (twice the limit of detection). Preharvest applications and in-crop applications in glyphosate tolerant crops can produce higher residue levels, resulting in MRLs > 0.1 mg/kg.

Residue decline studies were performed on glyphosate tolerant crops and showed a rapid decrease of the residue level from day 0 to harvest essentially due to plant growth and wash-off by rainfall. Typical dissipation pattern of glyphosate related residues in maize, sugarbeet and soybeans are given in appendix 3.

MRLs can also be set for imported commodities. They are determined from field residue trials with glyphosate in the country of origin.

4.3. Processing studies

Processing studies have been conducted with both non-tolerant and tolerant crops. Significant reductions in glyphosate residues occur in various processed fractions, including refined oils and sugar from sugar beet.

4.4. Metabolism in livestock

Metabolism studies have been conducted on lactating goats and laying hens to determine the metabolism, distribution and expression of residues in livestock. For both studies, no evidence was found for additional metabolites or for the accumulation of glyphosate or AMPA. Additionally the studies show that there is very little transfer of residues from feed to animal tissues and no bioaccumulation of residues occurs.

4. 5. Livestock feeding studies

Livestock feeding studies using glyphosate and AMPA were conducted with swine, poultry and lactating cows. For these studies, test groups of animals were fed a daily diet containing a 9:1 mixture of glyphosate and AMPA at total combined dietary levels of 40, 120 and 400 mg/kg for 28 days. The dosing levels represent respectively 1x, 3x and 10x of the maximum expected residue level of glyphosate and AMPA in the diet. The results show that glyphosate and AMPA do not transfer to animal tissues; at the expected 1x dose level, glyphosate residues were <0.05 mg/kg in all animal tissues and <0.025 mg/kg in milk and eggs.

4.6. MRL

On the basis of the submitted residue data of all relevant raw agricultural and processed commodities and of the maximum exposure levels of livestock to treated feedingstuffs, MRL proposal have been made by the EU and the CODEX Alimentarius Commission. In case of no detected residues in the examined crops, the MRL is fixed to 0.1 mg/kg (twice the detection limit in crops).

4.7. Dietary exposure

Appendix 1 lists the TMDI calculations based on the proposed MRLs and the mean food consumption (g/person/day) as described by the GEMS/Food Regional Diets (European diet – 1997)
Assuming that:

- all consumed food contains glyphosate residues of at least 0.1 mg/kg.
- the foods for which glyphosate has an MRL > 0.1 mg/kg contain residues at the MRL
- the glyphosate residue level in oil produced from oilseeds is set at the MRL for the seed, even though glyphosate is not detected in the refined oil
- all mushrooms (both cultivated and wild) contain glyphosate residues at 50 mg/kg, which is the MRL for wild mushrooms to account for possible overspray of wild mushrooms during forestry uses of glyphosate

the theoretical maximum daily intake reaches 17.13 % of the acceptable daily intake for glyphosate (which is 0.3 mg/kg body weight/day), still providing a large safety margin for the consumer.

To represent a more realistic worst case, the following refinements are proposed in Appendix 2:

- the cereals (which account for the major portion of the TMDI) contain residues at the Supervised Trials Median Residue (STMR) level
- the oil processing studies are taken into account (oil has glyphosate residues of only 0.1 mg/kg, which is the default MRL used when no glyphosate is detected)
- the mushrooms eaten are not wild mushrooms and contain glyphosate residues of 0.1 mg/kg, which is the MRL for cultivated mushrooms

In this case, the dietary exposure reaches only 3.2% of the ADI.

5. Impact of the introduction of glyphosate tolerant crops (RR soybeans, maize and sugar beet) on the dietary exposure

For soybeans and maize, the MRL for non-tolerant crops also covers the residues expected from glyphosate use in tolerant crops. No impact on dietary exposure based on TMDI is thus expected from those crops.
For sugar beet, the MRL has been raised from 0.2 mg/kg (for non-tolerant crop uses only) to 2 mg/kg (for both non-tolerant and tolerant crop uses).

Commodity	MRL (mg/kg) previous	MRL (mg/kg) new	Consumption (kg/person/day)	Increase in glyphosate intake (mg/person/day)
Sugar beet products	0.2	2	0.0988	0.1778

Increase in TMDI as a % of ADI = $\frac{0.1778 \times 100}{60 \times 0.3} = 1.0\ \%$

Under the worst case assumption that all the sugar beet are treated with glyphosate, and that all sugar is derived from sugar beet and contains residues at the MRL, the introduction of Roundup Ready sugar beet will increase the dietary exposure by only 1.0% of the ADI.
However, only a minimal amount of sugar beet enters the diet as such, with most being processed to sugar. Processing studies have been conducted on sugar beet and have shown that glyphosate residues are <0.05 mg/kg in sugar.

Commodity	MRL (mg/kg) previous	MRL (mg/kg) new	Consumption (kg/person/day)	Increase in glyphosate intake (mg/person/day)
Sugar beet	0.2	2	0.002	0.0036
Sugar[1]	0.1	0.1	0.0968	0.000
Total				0.0036

[1]Values listed for sugar are not MRLs, but maximum expected residue levels based set at twice the limit of detection

Increase in dietary intake as % of ADI = $\frac{0.0036 \times 100}{60 \times 0.3} = 0.02\ \%$

Taking into account the processing study done on sugar beet by setting the sugar residue level to 0.1 mg/kg, and differentiating the consumption data for sugar beet and sugar, the introduction of Roundup Ready sugar beet will only increase the dietary intake by 0.02%.

The impact of the introduction of these Roundup Ready-crops on the exposure of the consumer to glyphosate residues will thus be very marginal.

6. Conclusion

Glyphosate is used on a large variety of crops, but only a limited number of uses generate residues in the edible parts of the crops. Additionally, the acceptable daily intake is quite favorable, in line with the toxicological properties of the compound.
The dietary exposure calculations show that under the unrealistic worst case scenario where all the crops, fish, seafood and animal products would contain residues at the maximum residue level or at 0.1 mg/kg if no current MRL exists, the consumer would only ingest 17% of the glyphosate acceptable daily intake.
No impact on human health is thus to be expected for the consumer of food treated with glyphosate according to good agricultural practices.

Appendix 1 : TMDI from glyphosate residues in food

Food	Consumption (kg/person/day)	Residue level[1] (mg/kg)	Daily Intake (mg/person)
CEREALS			
Barley	0.0198	20	0.396
Maize	0.0088	1	0.0088
Oat	0.0020	20	0.04
Rye	0.0015	20	0.03
Wheat	0.1780	10	1.78
Rice	0.0118	0.1	0.00118
Others	0.044	0.1	0.00044
ROOT AND TUBERS			
Potatoes	0.2408	0.5	0.1204
Others	0.0012	0.1	0.00012
PULSES			
Beans	0.0043	1	0.0043
Peas	0.0028	5	0.014
Soybeans	0	20	0
Others	0.005	0.1	0.0005
SUGARS AND HONEY			
Sugar beet	0.002	0.2	0.0004
Sugar (refined)	0.0968	0.1	0.00968
Others	0.0085	0.1	0.00085
NUTS AND OILSEEDS			
Total nuts and oilseeds	0.0299	0.1	0.00299
VEGETABLE OILS[2]			
Maize oil	0.0013	1	0.0013
Linseed oil	0	10	0
Olive oil	0.0078	20	0.156
Rapeseed oil	0.0073	10	0.073
Soybean oil	0.0043	20	0.086
Others	0.0179	0.1	0.00179
STIMULANTS			
Tea	0.0023	2	0.0046
Others	0.0121	0.1	0.00121
SPICES			
All spices	0.0005	0.1	0.00005

VEGETABLES			
Mushrooms[3]	0.004	50	0.2
Other vegetables	0.3678	0.1	0.03678
FISH AND SEAFOOD			
Total	0.0463	0.1	0.00463
FRUITS			
Citrus fruits	0.049	0.5	0.0245
Grapes	0.0161	0.5	0.00805
Other fruits	0.1473	0.1	0.01473
ANIMAL PRODUCTS			
Milk products	0.3408	0.1	0.03408
Eggs	0.0375	0.1	0.00375
Meat and offal	0.2173	0.1	0.02173
Animal oils and fats	0.0107	0.1	0.00107
TOTAL ($\Sigma F_i \times MRL_i$)			3.08293

[1]Residue level set at the MRL, or at 0.1 mg/kg if no MRL exists

[2]Residue level for oils set at the MRL for the whole oilseed

[3]Residue level for mushrooms set at MRL for wild mushrooms

$$TMDI = \frac{\Sigma F_i \times MRL_i}{Bw} = \frac{3.08293}{60} = 0.0514$$

$$\% \text{ of ADI} = \frac{0.0514 \times 100}{0.3} = 17.12\ \%$$

Appendix 2 : Realistic worst case dietary intake

Food	Consumption (kg/person/day)	Residue level[1] (mg/kg)	Daily Intake (mg/person)
CEREALS[2]			
Barley	0.0198	**4.65**	**0.09207**
Maize	0.0088	**0.1**	**0.00088**
Oat	0.0020	**5.4**	**0.0108**
Rye	0.0015	**3.86**	**0.00579**
Wheat	0.1780	**0.85**	**0.1513**
Rice	0.0118	0.1	0.00118
Others	0.044	0.1	0.00044
ROOT AND TUBERS			
Potatoes	0.2408	0.5	0.1204
Others	0.0012	0.1	0.00012
PULSES			
Beans	0.0043	1	0.0043
Peas	0.0028	5	0.014
Soybeans	0	20	0
Others	0.005	0.1	0.0005
SUGARS AND HONEY			
Sugar beet	0.002	0.2	0.0004
Sugar (refined)	0.0968	0.1	0.00968
Others	0.0085	0.1	0.00085
NUTS AND OILSEEDS			
Total nuts and oilseeds	0.0299	0.1	0.00299
VEGETABLE OILS[3]			
Maize oil	0.0013	**0.1**	**0.0013**
Linseed oil	0	**0.1**	**0**
Olive oil	0.0078	**0.1**	**0.00078**
Rapeseed oil	0.0073	**0.1**	**0.0073**
Soybean oil	0.0043	**0.1**	**0.00043**
Others	0.0179	0.1	0.00179
STIMULANTS			
Tea	0.0023	2	0.0046
Others	0.0121	0.1	0.00121
SPICES			
All spices	0.0005	0.1	0.00005

VEGETABLES			
Mushrooms[4]	0.004	**0.1**	**0.0004**
Other vegetables	0.3678	0.1	0.03678
FISH AND SEAFOOD			
Total	0.0463	0.1	0.00463
FRUITS			
Citrus fruits	0.049	0.5	0.0245
Grapes	0.0161	0.5	0.00805
Other fruits	0.1473	0.1	0.01473
ANIMAL PRODUCTS			
Milk products	0.3408	0.1	0.03408
Eggs	0.0375	0.1	0.00375
Meat and offals	0.2173	0.1	0.02173
Animal oils and fats	0.0107	0.1	0.00107
TOTAL ($\Sigma F_i \times MRL_i$)			**0.5751**

[1]Residue level set at the MRL, or at 0.1 mg/kg if no MRL exists, except for cereal grains and oils

[2]Residue level for cereal grains set at the STMR

[3]Residue level for oils set at 0.1 mg/kg

[4]Residue level for mushrooms set at MRL of cultivated mushrooms

$$\text{Total intake} = \frac{\Sigma F_i \times MRL_i}{Bw} = \frac{0.5751}{60} = 0.0096$$

$$\%\text{ of ADI} = \frac{0.0096 \times 100}{0.3} = 3.2\ \%$$

Appendix 3 :

Figure 1 :
Glyphosate residue dissipation in RR-maize plants following a typical RoundupReady® herbicide treatment scheme
Line NK603 – Site : L'Isle Jourdain – France 2000

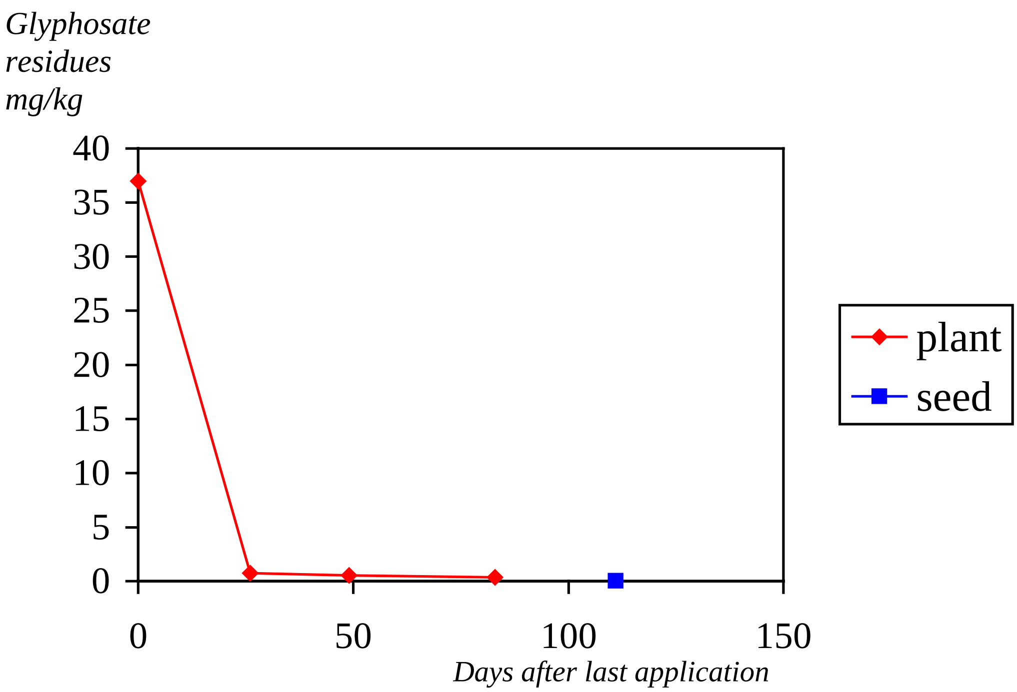
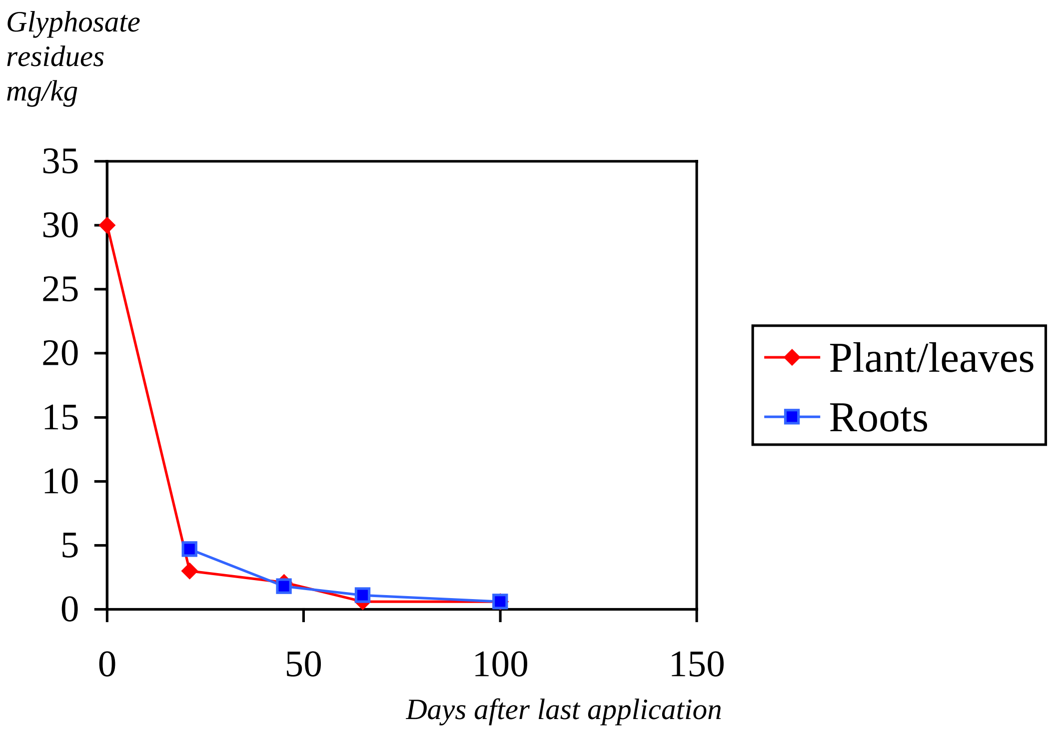


Figure 2 :
Glyphosate residue dissipation in RR-sugarbeets following a typical Roundup Ready® herbicide treatment scheme
Line #77 – Site : Villers Cotterêts – France 1996



<u>Figure 3 :</u>
Total* glyphosate residue dissipation in RR-soybeans following a typical Roundup Ready® herbicide treatment scheme
Line 40-30-2 – Site : Monbequi –France 1995

(* Total residue = glyphosate + AMPA expressed as glyphosate equivalent)