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REGISTRATION OF PLANT PROTECTION PRODUCTS: EMERGING ISSUES

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Maximum residue levels: a critical investigation

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ABSTRACT

Maximum residue levels (MRLs) are trading standards that represent the maximum residue that could be found if a crop protection product (CPP) is applied according to good agricultural practice (GAP). Foodstuffs are monitored for MRL compliance and exceedence can have serious consequences. When setting MRLs, a balance is required between setting the MRLs sufficiently low to prevent misuse and sufficiently high to prevent a farmer being unfairly penalised for exceeding the MRL by chance. This study investigates how the two current EU MRL calculation methods address this balance. The shape and parameters of the residue distribution, limit of quantification and number of trials all affected the accuracy and precision of the estimated MRL. Both methods were least accurate and precise at small numbers of trials and high coefficients of variation, with up to four different MRLs possible. Eight to 16 trials gave the best estimate of the MRL, but exceedence by chance could occur in up to 40% of samples. 'Best practice' for use of the methods is to calculate the MRL by both methods and take the highest.

INTRODUCTION

Maximum residue levels (MRLs) are international trading standards that represent the maximum residue level that should be found on a foodstuff if a crop protection product (CPP) is applied according to good agricultural practice or GAP (i.e. the maximum application rate and number of applications and the minimum pre-harvest interval) (FAO/WHO, 1997). Monitoring programmes target specific agricultural produce, especially imports, to test their compliance with MRLs. Any residue greater than the MRL results in the produce being rejected and repeated exceedence can lead to international trade problems. Exceedence may also cause social and political pressure for reduced crop protection product (CPP) inputs and reinforce beliefs that CPPs are unsafe despite the fact that the MRL is a legal limit not a health standard. MRLs are always set below levels that are of toxicological relevance for consumers (FAO/WHO, 1997) and are used in the evaluation of chronic dietary exposure, as part of an initial screening procedure.

Accurate estimation of the MRL is very important. If an MRL is set too high then misuse of CPPs may go undetected. However, if an MRL is set too low then farmers who follow GAP may be unfairly penalised. The European methods for calculating MRLs could be inaccurate due to: (1) large variability in residues (Ambrus, 2000); (2) error in parameters estimated from small data sets (4 - 16 points); (3) distributions of residues are often positively skewed (Ambrus, 2000); (4) censored data are incorporated in estimates, as the residue distribution is truncated at the limit of quantification (LOQ) and the residue at the LOQ is used in the

calculation (Helsel, 1990); and (5) the calculated value is rounded to the next 'MRL Class' (EC, 1997).

In this study, simulations are used to investigate: (1) the accuracy of existing European MRL calculation methods; (2) the probability of exceedence of the MRL by chance; and (3) best practice for using these methods to control exceedence of the MRL by chance whilst preventing misuse.

EUROPEAN MRL CALCULATION METHODS

Residue data are collected from supervised field trials where CPPs are applied according to GAP. The number of trials required depends upon the consumption and production of the crop in Northern and Southern Europe. Generally, between four (for a minor crop in either North or South region of Europe, but not both) and 16 (for a major crop in both regions of Europe) trials are conducted. For the calculation, any non-detectable residues are assumed to be at the limit of quantification (LOQ).

There are two methods used to calculate MRLs (EC, 1997). Method I assumes that residues are normally distributed and a one-sided 95% tolerance interval is calculated (EC, 1997). Thus, it is asserted with 95% confidence that 95% of all residues are less than the MRL. Method II is a distribution free method and is calculated by doubling the 75th percentile of the field trial residue data. This figure characterises a value that is not exceeded in 75% of cases and doubling it represents a safety margin (EC, 1997). MRL classes have been defined, and the calculated MRLs are rounded to the next class (see Table 1).

The regulatory guidelines are not specific about when each method should be used (EC, 1997). The main recommendations are that neither method should be used for data sets with less than eight trials (although MRLs must still be calculated) and Method II should not be used with less than eight to 12 trials.

SIMULATION METHODS

Simulations were done using the method shown in * MERGEFORMAT Figure 1. Residues were selected at random from an underlying distribution and residues less than the LOQ were considered to be at the LOQ. These residues were used to calculate MRLs using EU Methods I and II. This process was repeated 10,000 times to give distributions of MRLs calculated using both methods. This was done with the MRL both before and after rounding to the next MRL class (Table 1).

Table 1: The 16 MRL classes (mg/kg). MRLs are generally set at one of these values.

0.01	0.02	0.05	0.1	0.2	0.3	0.5	1
2	3	5	10	20	50	100	> 100

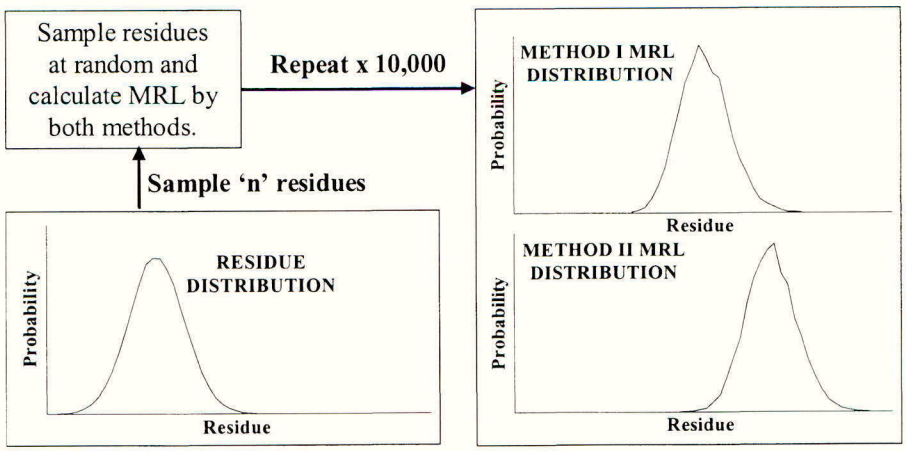

Figure 1: Method used for simulating MRLs. Residues were selected at random from an underlying distribution and MRLs calculated. This process was repeated 10,000 times to produce distributions of MRLs calculated using Methods I and II.

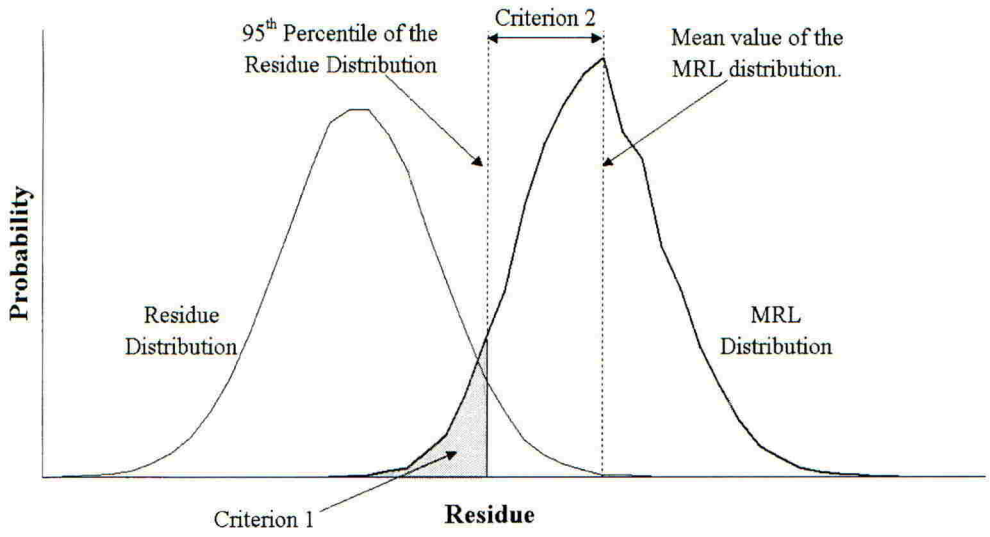

Figure 2: Assessment criteria for MRL calculation methods. Criterion 1 measures chance exceedence where a 'good' method is defined as having at most a 5% chance that the calculated MRL is less than the 95th percentile of the residue distribution. Criterion 2 measures the potential for misuse, where a 'good' method is defined as the mean of the MRL distribution is not more than 2 times the 95th percentile of the residue distribution.

Simulations were used to highlight the problems with each method, investigate the effects of MRL classes, and define best practice for use of the methods. The parameters and shape of the residue distribution and the LOQ were varied in the simulations. The results were assessed by probability of exceedence (Criterion 1) and the potential for misuse (Criterion 2) (Figure 2).

RESULTS

The residue distribution shape, LOQ and the number of trials all affected the calculation of the MRL, with both methods I and II being least accurate and precise at small numbers of trials and high residue variability. Using a single set of parameters, the calculated MRL could fall in up to four MRL classes.

The optimum number of trials required was dependent upon the underlying residue distribution and the imposition of MRL classes, but was generally between 8 and 16. The spread of the MRL distribution was larger for lognormally than normally distributed residues.

Exceedence by chance was defined as the proportion of the underlying residue distribution that is greater than the MRL. Up to 40% exceedence was possible in simulations with realistic parameters. The 'best practice' for controlling exceedence and misuse with the existing MRL

methods was to calculate the MRL using both methods and take the highest. However, even this policy often had high probabilities of exceedence.

DISCUSSION

Both methods resulted in less accurate estimates of the MRL for small numbers of trials and high coefficients of variation (CV = standard deviation / mean) as parameter estimates from small data sets are subject to large errors. MRL classes affected the probability of calculating the correct MRL. This was especially important when the MRL calculated was close to the boundary between classes as small differences in the mean and standard deviation caused the selection of different MRL classes. In fact, the MRL could be located in up to four separate classes at high CVs and low numbers of trials.

Exceedence of MRLs provides newspaper headlines, despite rarely indicating a health risk. Annual monitoring of MRLs shows that exceedence is about 4% (EC, 2001). However, over 25% exceedence has been found for a single commodity (EC, 2001), which is within the 40% observed in these simulations. Thus, in reality, exceedence could be due to misuse or by chance. In recent years, the GAP has been set at a level that is closer to the amount of CPP required to provide adequate control, whilst preventing resistance. If the difference between rates applied by the farmer and the GAP decreases, then exceedence of the MRL by chance could become more common. Best practice was to calculate the MRL by both methods and use the highest, but chance exceedence was still high.

Where many residues are less than the LOQ, a new method for MRL calculation could be developed based on maximum likelihood methods used to account for censored data in estimates (Helsel, 1990).

For a complete analysis of the methods for calculating EU MRLs and the 'best practice' for using these methods see Hyder *et al.* (2003).

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The effects of refining consumer exposure assessments of glyphosate

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ABSTRACT

The dietary risk assessment based on worst-case consumer exposure scenario, conducted as part of the EU review leading to Annex I inclusion of glyphosate was evaluated. An extensive database of information on the effects of processing on the levels of glyphosate residues in food is available. This database, together with refined consumption data from the UK's surveys of adults and toddlers and extensive monitoring data of glyphosate residues in cereals conducted in the UK were combined to examine the potential over-estimates of consumer exposure that are predicted using the current regulatory methodology. This analysis focused on exposure from treated cereals, the crop group contributing significantly to the glyphosate intake by the consumer. Calculations using the most unrefined methodology gave rise to intakes of up to only 11% of the acceptable daily intake (ADI); this was reduced to 0.6% of the ADI when justifiable refinements based on extensive monitoring data collected in the UK were made. Consumption data for processed foods abstracted from the UK Food Standard Agency's database were used to try to include further changes in the consumer exposure model from residue concentrations resulting from processing.

INTRODUCTION

Glyphosate, N-phosphonomethyl glycine, is a broad-spectrum non-selective herbicide, widely used for post-emergence control of annual and perennial weeds. It is approved throughout Europe for a range of agricultural uses, including pre-emergence and pre-plant applications to various vegetables and arable crops, directed application to weeds in orchards and vineyards, and pre-harvest application in pulses, oilseeds and cereals. Some of the use patterns of glyphosate can lead to detectable residues. Current risk assessment methodology for determining long-term exposure to pesticide residues uses the supervised trials median residues (STMRs – the median residue value obtained from supervised trials) taking account of any processing factors (PFs; i.e. any changes in residues concentration as a result of processing). In an FAO/WHO consultation, it was also considered acceptable to use monitoring data in risk assessments although, apart from in the US, this practice is not frequently carried out (WHO, 1995). This paper looks at the refinements to dietary exposure that are possible, progressing to the most realistic deterministic assessments but without using probabilistic modelling, and focusing on exposure from treated cereals, the crop group contributing significantly to the glyphosate intake by the consumer.

MATERIALS AND METHODS

Standard chronic assessment method

Standard chronic consumer exposure assessments were carried out using STMRs and PFs derived from the EU review of glyphosate (Glyphosate Monograph) (Table 1 and 2) and consumption values for toddlers and adults derived from the UK's Pesticides Safety Directorate database (PSD, 2001) (Table 3).

Table 1. The range of glyphosate residues detected in supervised trials reviewed under Directive 91/414

Commodity (grain)	residue (mg/kg)		
	min	max	STMR
barley	0.9	21	4.65
oat	0.3	21.4	5.4
rye	1.9	16.7	3.9
wheat	<0.05	16.9	0.85
maize	<0.05	2.6	0.1

Table 2. Processing factors (PF) for glyphosate residues detected in supervised trials reviewed under Directive 91/414

Raw commodity	barley	barley	oats	wheat	wheat	wheat	wheat	maize
Processed commodity	malt	beer	groats	bran	white flour	white bread	wholemeal flour	oil
n	61	17	17	15	12	8	5	4
min	0.01	0.005	0.1	1.6	0.04	0.03	0.1	0.01
max	0.5	0.07	0.8	3.6	0.8	0.09	0.9	0.03
mean	0.16	0.03	0.44	2.23	0.26	0.06	0.54	0.02
STMR-p (mg/kg)	0.74	0.14	2.4	1.9	0.22	0.05	0.46	0.002

Table 3. Consumption values published by the Pesticides Safety Directorate (kg/person/day)

	Adult		Toddler	
	Mean	97.5th percentile	Mean	97.5th percentile
Wheat	0.1395	0.25	0.0529	0.1053
Barley (assuming barley comprises of 1% beer consumption)	0.0023	0.0236	L/C	0.0037
Oats	0.0029	0.0409	0.0018	0.0197
Maize (Cornmeal)	0.001	0.0343	0.0021	0.0163
Bran	0.0034	0.0572	0.0045	0.0360

L/C = low consumption (less than 60 consumers in the survey)

Refined chronic assessment using abstracted consumption data

A second set of calculations was carried out, substituting the consumption data used above, with abstracted consumption data obtained from the actual food forms available from the raw data stored at the Food Standard Agency's archives at the University of Essex (Gregory *et al.*, 1990; Gregory *et al.*, 1995) (Table 4).

Table 4. Per capita consumption of cereal by UK toddlers (n = 1675) and adults (n = 2192) (4-day averages, kg/person/day)

	Toddlers		Adults	
Cereal	Mean	97.5th Percentile	Mean	97.5th Percentile
Barley - Beer	<0.0001	0.0000	0.0297	0.2159
Barley - Grain	0.0004	0.0017	0.0004	0.0023
Barley - Malt	0.0000	0.0000	0.0000	0.0003
Maize - Grain	0.0062	0.0265	0.0156	0.0754
Maize - Grain (including HFCS)	0.0343	0.0746	0.0452	0.1212
Maize - Oil	0.0010	0.0025	0.0019	0.0045
Oat - Bran	0.0000	0.0000	0.0000	0.0000
Oat - Grain	0.0014	0.0129	0.0009	0.0100
Oat - Groats	0.0002	0.0035	0.0004	0.0046
Wheat - Bran	0.0003	0.0042	0.0019	0.0229
Wheat - Flour	0.0357	0.0773	0.0726	0.1762
Wheat - Grain	0.0108	0.0447	0.0293	0.1147

HFCS = high fructose corn syrup

Further refinement of chronic assessment using monitoring data

The final intake assessments were carried out using a range of residues data: STMRs and STMR-ps taken from the review carried out under Directive 91/414 and pesticide residues monitoring data from the UK's Pesticides Residues Committee studies which were carried out between 1998 when glyphosate was first introduced into the monitoring programme for cereals and 2002 (WPPR, 1999; WPPR, 2000; PRC, 2001; PRC, 2002; PRC, 2003). PRC data are summarised in Table 5.

Table 5. Glyphosate residues detected in retail products in monitoring by the Pesticide Residues Committee

Year	Crop	Detectable residues			Glyphosate mg/kg; (no. of samples)	Mean detectable residues (mg/kg)	Median residues (mg/kg)
		UK	imp	unk			
2000-2	bread - brown	4/53			0.1 (3), 0.3	0.15	<0.1
2001	bread - granary	0/5				<0.1	<0.1
2002	bread - other	10/16		0/2	0.1 (4), 0.2 (6)	0.16	0.1
2002	bread - part baked	0/36	0/6	0/6		<0.1	<0.1
2001-2	bread - savoury	4/63			0.1 (2), 0.2 (2)	0.15	<0.1
2000-2	bread - white	8/248		0/6	0.1 (5), 0.2, 0.3, 0.4	0.2	<0.1
2000	bread - wholemeal	20/62		0/1	0.1(14), 0.2 (5), 0.3 (1)	0.1	<0.1
2001-2	bread -ordinary	6/221			0.1 (3), 0.2 (3)	0.15	<0.1
2000-1	bread-multigrain	3/18			0.1, 0.2, 0.3	0.2	<0.1
2001	bread-softgrain	0/5				<0.1	<0.1
2002	flour - white	0/46		0/1		<0.1	<0.1
2002	flour - wholemeal	7/24			0.1, 0.2 (3), 0.3 (2), 0.4	0.24	0.1
2002	flour -rye	0/1				<0.1	<0.1
1999	barley	1/43		0/1	0.5	0.5	<0.1
2001	bran	34/47			0.1-0.5 (17), 0.6-1.0 (13), 1.2-1.8 (4)	0.66	0.4
1998	maize		0/16	0/5		<0.1	<0.1
1999	millet	0/1	0/6			<0.1	<0.1
1998	oats	2/12		0/8	0.3, 2.8	1.6	<0.1
1999	rye	0/17				<0.1	<0.1
1999	triticale	0/9				<0.1	<0.1
1998	wheat	1/38		2/21	0.2 (UK), 0.3, 0.6 (unk)	0.37	<0.1
2001	breakfast cereals	3/28	0/2	12/66	0.2 (2), 0.4 (UK), 0.1-0.3 (12) (unk)	0.22	<0.1
2001	cereal bars	0/14	0/17	4/66	0.1 (3), 0.2	0.1	<0.1
2002	infant food –cereal based	0/5	0/16	0/52		<0.1	<0.1
2001	noodles (wheat and rice)		0/2	0/46		<0.1	<0.1
1999	pasta	0/13	0/58	0/1		<0.1	<0.1
2002	polenta	0/2	3/31	3/11	0.1 (6)	0.1	<0.1
2002	popcorn			0/21		<0.1	<0.1

UK = UK origin, imp = imported, unk= unknown country of origin

RESULTS

In general, intakes were calculated using the Rees-Day methodology (PSD 2001), that combines intake values to give an approximation of dietary intake at the 97.5th percentile level. This is achieved by calculating the 97.5th and mean intake for each individual commodity and then combining the highest two intakes at the 97.5th percentile plus the mean intakes from the other commodities (PSD, 2001). Mean body weights from the surveys were used: 70.1 kg for adults and 14.5 kg for toddlers (PSD, 2001).

Applying this methodology, intakes were calculated using either, the consumption data from PSD, or using abstracted data. Since there were differences between the commodities considered, efforts were made to link residues concentrations as closely as possible to similar commodities. This was to minimise any effects that may occur as a result of the use of different residue concentrations for particular processed products that could fall in to one or more categories in the calculation.

Calculated intakes were as shown in Table 6 and Figure 1. Where residues were below the limit of quantitation (0.1 mg/kg), intakes have been calculated conservatively assuming that residues occur at the limit of quantitation. The acceptable daily intake for glyphosate was set at 0.3 mg/kg bw/day (EU Review Report (European Commission, 2002a)

Table 6. Calculated intakes (mg/kg bw/day) of glyphosate by UK adults and toddlers based on a range of residues data and 2 highest intake contributors

	intakes				Highest contributors to intake			
residues data utilised	AD adults	AD toddlers	PSD adults	PSD toddlers	AD adults	AD toddlers	PSD adults	PSD toddlers
STMR	0.0171	0.0107	0.0094	0.0239	Beer, wheat flour	Oats, wheat flour	Bran, oat grain	Oats and bran
STMR-p	0.0022	0.0080	0.0115	0.0334	Oats, wheat flour	Oats , wheat flour	Wheat and bran	Wheat and bran
mean mon	0.0025	0.0035	0.0023	0.0051	Beer, wheat flour	Oats, wheat flour	Wheat and oats	Wheat and oats
mean mon-p	0.0009	0.0021	0.0013	0.0051	Wheat flour and maize	Wheat flour and maize	Wheat and bran	Wheat and bran
median mon	0.0007	0.0014	0.0007	0.0017	Wheat flour, beer	Wheat flour, maize	Wheat and bran	Wheat and bran

AD = abstracted data, PSD = PSD data, mon = monitoring data from WPPR/PRC surveys

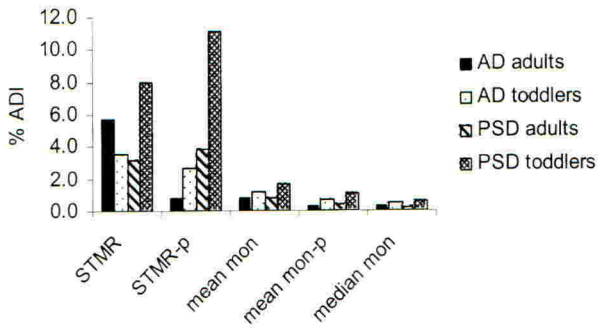

Figure 1. Intakes of glyphosate expressed as a percentage of the acceptable daily intake

DISCUSSION

The developments in methodology for calculating dietary exposure have progressed significantly over the last decade (Harris *et al.*, 2001), with the aim of obtaining the most realistic estimates possible, whilst still utilising simplistic methodology. Many countries throughout the world collect monitoring data on a regular basis giving a realistic view of the residues that are present in foods generally in commerce, as opposed to measured residues arising from supervised trials. Residues detected in these monitoring studies were often a fraction of those detected in supervised trials. Many foodstuffs are not consumed in a raw form, particularly in the case of cereals, and further refinements can be made using processing factors. The WHO recommended in their review of methodology for intake of pesticide residues that refining criteria, such as processing factors should be taken into account where relevant in all predictions of consumer exposure (WHO, 1995). They also recommended that if sufficient numbers of data points were available from monitoring studies, that these could be used in the assessment of consumer exposure. To date, this does not appear to be a regular practice in Europe. However, the European Commission have recently commissioned a study to look at more realistic exposure assessments based on monitoring data collected between 1996-2001, using a harmonised methodology (European Commission, 2002b).

This study looks at two factors in assessing consumer exposure – the selection and choice of the food forms used in calculating dietary exposure and the use of progressively refined residues data.

Glyphosate is supported by an extensive residues data package which is far in excess of the minimum requirements laid down by regulatory authorities (PSD, 2001). The residues data from supervised trials indicate that a wide range of residues were detected and these residues are greatly reduced as a result of processing. This is a pattern that would be expected with a highly water soluble compounds such as glyphosate. Residues in cereal products both processed and unprocessed from the UK supply chain show residues that are significantly lower than those predicted by regulatory data, even though the actual residue levels are overestimated, because of a relatively high limit of quantification (0.1 mg/kg). Intakes were calculated using the standard UK model developed by PSD – this gives consumption values for

raw agricultural commodities and does allow for the use of processing factors but only a single processing factor can be applied to each processed commodity. We have extracted consumption data from the individual consumption records based on the data collected by Gregory *et al.*, (1990 ,1995) linking the consumption to the processed fractions where data exist, to allow as many refinements as are supported by data. To ensure that consumption was not biased, where a foodstuff did not automatically fall into one of the processed categories where additional food forms existed, additional contributions were included with the grain fraction. On occasions, data have been included in the abstracted dataset for certain food forms which do not appear in the PSD model. When consumption data for processed foods are abstracted from raw FSA data for use in the PSD deterministic models, a cut-off of 5% occurrence in recipes was applied i.e. consumption was not included unless it formed at least 5% of a recipe.

In calculating intakes using both sets of consumption data, the Rees-Day model was used to combine intakes to provide an approximation of the total dietary intake of glyphosate via the consumption of cereal products. When intakes were calculated using monitoring data, food forms were linked as closely as possible.

Intakes were highest for toddlers in all cases with the exception of the use of the STMR and abstracted data model.

The steep reduction of predicted intake seen when progressively realistic measures of residues were incorporated into the models gives a strong indication of the conservative nature of the regulatory procedures.

The PSD model consistently predicted the highest intakes, with the exception of intakes by adults using the STMR and median monitoring data. This suggests that conservatism in the regulatory model exists where specific processing factors cannot be applied to specific fractions of the diet.

The difference in intake calculated using the mean residue obtained from monitoring taking account of the effects of processing and the median residue from monitoring data gives a good indication of the effect of the limit of quantitation in the calculation of intake. Where the limit of quantification does not affect the residue concentration used i.e. the median residues, intakes were 1.5-2.9 times lower than those calculated using the mean residue adjusted for processing changes.

Whilst this indicates that the choice of consumption scenario and residues data can affect the overall predicted intake of glyphosate residues, even the most conservative model resulted in an intakes of up to only 11% of the acceptable daily intake. The most refined calculations gave intakes of a maximum of 0.6% of the acceptable daily intake giving an overall safety factor of greater than 17,000 against the no effect level seen in studies used to derive the acceptable daily intake (EU Review Report (European Commission, 2002a).

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Cooperative facilitation of registrations of crop protection chemicals in fruits, vegetables and other specialty crops in the United States and Canada

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ABSTRACT

Growers of minor crops (fruits, vegetables, herbs and other specialty crops do not always have legal access to safe and effective pest control technology. This is mainly due to the economic factors; the cost of data development for the registrant often exceeds the potential return on investment. In the United States, Interregional Regional Research Project Number Four (IR-4) was established to support the regulatory approval for many of the needed crop protection chemicals on minor crops. IR-4 is a co-operative partnership between the US Federal government, state agricultural experiment stations, crop protection industry, commodity organizations and minor crop farmers to provide to develop the necessary data. Minor crop growers in Canada have the similar challenges in getting access to crop protection chemicals. IR-4 has been working with its counterparts in Canada to develop data collaboratively. In spring 2002, the Canadian government made a large financial commitment to upgrade the research and regulatory infrastructure to support the clearance of minor use crop protection chemicals. It is envisioned that the two programs in North America will significantly increase their collaboration in the future.

MINOR USE CLEARANCE PROCESS IN UNITED STATES

Interregional Research Project Number Four (IR-4) was established in 1963 by the United States Department of Agriculture (USDA) to obtain regulatory approval for crop protection chemicals on fruits, vegetables, herbs and other specialty crops when the economic incentive for the private sector, the chemical company registrants, often limits their financial investment. The Directors of the State Agriculture Experiment Stations provided the stimulus for the establishment of IR-4. The fundamental problem was growers of the fruits, vegetables, herbs and other specialty crops (collectively called minor crops) do not always have legal access to safe and effective pest control technology.

In 1977, IR-4's mission was expanded to include facilitation of registrations of crop protection chemicals on nursery, floral, forestry seedling, Christmas trees and turf grass, crops. The mission was further expanded in 1982 when the objective of gaining clearance of biological pest control agents was added.

IR-4 operates as a unique partnership between the State Universities (also known as land grant universities) system in the United States, USDA, commodity growers and crop protection chemical companies, to accomplish its goal to provide crop protection solutions for minor crops. The IR-4 Project is managed by a headquarters staff which is located at Rutgers University in New Jersey, a USDA-Agriculture Research Service (USDA-ARS) co-ordinator in Beltsville, Maryland, and four regional offices that are associated with University of California-Davis, California; University of Florida-Gainesville, Florida; Michigan State University-East Lansing, Michigan; and Cornell University-Geneva, New York. All these units operate independently under the umbrella of the IR-4 Project Management Committee (IR-4 PMC). The IR-4 PMC meets on a regular basis to review the status of on-going programmes, develop policy and procedures, set operational budgets, develop strategic plans and ensure that the programmes overall goals are being met. Stakeholders have a strong voice in IR-4 management through the efforts of the Commodity Liaison Committee (CLC). The CLC serves as a bridge between IR-4 and the growers of minor crops to assure that the programme continues to focus on significant pest management problems. They also serve a role to provide guidance and advice on ways in which the programme can best serve the needs of minor crop commodity producers. Another important CLC role is to support federal IR-4 funding and budget support initiatives to help secure stable [sources][provision] of resources. The Chair of the Commodity Liaison Committee serves as a non-voting member of the Project Management Committee.

Most requests for IR-4 assistance come from federal and state researchers/extension scientists involved in minor crop pest management. IR-4 also receives requests directly from growers and/or organizations representing a commodity. The only IR-4 stakeholders prohibited from submitting requests are representatives of agricultural chemical companies. A request for assistance consists of the completion and submission of a simple one-page Project Clearance Request (PCR) form. Completed forms can be submitted electronically via the IR-4 web site at http://www.cook.rutgers.edu/~ir4. This form seeks some basic information, such as the crop, the proposed pest management tactic, the target pest(s) in question, the proposed use of the pest management tool, including the application rate and timing, the interval from last treatment to harvest and why the pest control material is needed. The form also enquires if any preliminary data are available. Preliminary data are very important because they are often needed to convince the agricultural chemical companies that the proposed use is safe when used on the crop and it effectively controls the target pests.

Upon receipt of the completed PCR, IR-4 personnel will determine if the proposed use already registered. If not, an enquiry will be sent to the agricultural chemical company that holds the US registrations for the requested chemical to determine if they are willing to cooperate with IR-4 to obtain the regulatory clearance of the pest control tool. Finally, IR-4 questions the US Environmental Protection Agency (US EPA) to query if there any regulatory impediments known that may delay or result in denial of the registration. If the company is willing to register the proposed use once IR-4 develops the appropriate data the proposed use is regarded as "Researchable" and is considered in the research project prioritization procedures.

Unfortunately, IR-4 does not have sufficient resources to conduct research on all proposed researchable projects. In fact, for every research project that IR-4 funds, there are approximately five projects delayed pending additional resources. Because of this shortfall, IR-4 strives to work on the most important projects. The Food Use and Ornamentals Workshops are the cornerstone of the IR-4 prioritization process. These are open fora where

over 200 minor crop growers, commodity organization representatives, agricultural chemical company representatives, and federal and state research/extension scientists attend and participate. At the workshops, every potential project is discussed in detail and its importance is considered on the basis of such factors as the availability and efficacy of alternatives, pest damage potential, performance of the proposed chemical, and its compatibility with integrated pest management programmes. From the workshop participants, three tiers of priorities for projects are identified. Priority A, the highest tier, are the most important projects. Because of their importance and to better service the needs of the minor crop growers, IR-4 will begin research work at the next practical experimental start date. All efforts will be made to submit results of Priority A research to US EPA within 30 months of protocol approval. The next tier projects, Priority B, are also important, but funding may not be available. IR-4 will use its resources in the most efficient manner to complete as many of these projects as soon as possible, given funding restraints. The final tier projects, Priority C, are considered of less importance than Priority A and Priority B projects. IR-4 will conduct research on these projects only after all Priority A and Priority B projects are conducted.

Though IR-4 follows the priorities set at the workshops very closely, there are occasions when the US EPA or the co-operating agricultural chemical company will recommend that IR-4 delay initiation of research for a specific chemical. IR-4 usually heeds this advice and either delays or cancels research pending satisfactory handling of the outstanding issue(s).

For food crops, the US EPA has published specific guidelines on the extent of residue field trials to be conducted in specific geographic regions of the country. These guidelines are based on the area of crop grown, along with the potential for dietary exposure, and centered on the major production regions for the crop. In addition, the US EPA requires that this research be conducted and documented following exacting procedures outlined in the US EPA Good Laboratory Practice (GLP) guidelines. All IR-4 research on food crops is conducted following very specific research directions outlined in a research protocol. This protocol contains directions for the receipt and handling of the test chemical, the application of the test chemical on the target crop, the harvesting of the mature crop at the appropriate harvest time, the collection of representative crop samples and handling of these samples after harvest, the transfer of the crop samples to the analytical laboratory, and the analysis of crop and other supporting residue samples.

In order to best meet the above requirements and to complete the research, IR-4 has established 31 field research centers at strategic locations throughout the United States. In addition, IR-4 has a network of four regional, three ARS and five satellite analytical laboratories that determine the amount of residues remaining in the crop. All these field centers and analytical laboratories operate under GLP. For non-food crops, the GLP guidelines are not required. In these studies, general protocol use directions are issued and the research co-operators apply the test chemical to the ornamental crops and monitor for pest control and/or an indication that the test chemical caused damage to the plants. All data from IR-4 sponsored studies are transferred from the field sites and/or analytical laboratories to the IR-4 Headquarters. Before the data are transferred, they are subjected to both quality control and quality assurance audits. These quality checks have helped ensure that IR-4 has achieved some of the lowest number of review cycles of any data submitter to US EPA. Once at IR-4 Headquarters, the Study Directors critically review the data and reformat it into a style required for submission and review by the co-operating agricultural chemical company and the US EPA.

The first step in obtaining the regulatory clearance for a proposed IR-4 food use is for IR-4 to submit the data to the US EPA. Upon receipt, US EPA Registration Division personnel perform a preliminary review for completeness of the data and start discussions with scientists in the Health Effects Division to schedule a comprehensive review of the IR-4 and supporting data from the agricultural chemical company. The data are reviewed and if they show that clearance of the use would not expose consumers or the environment to unreasonable adverse effects, the EPA publishes a tolerance as a Final Rule in the Federal Register. This tolerance is the maximum residue limit (MRL) of the agricultural chemical in or on the crop that is considered safe and legally acceptable.

For non-food crops, the process is much simpler because a tolerance is not required. The co-operating company can add the ornamental crop(s) to their registration once it feels comfortable that the use is safe to the crop and effective against the pest. The ultimate goal of IR-4's efforts is to facilitate new registrations of safe and effective pest control tools. However, to register the uses for both food and non-food crops, it is the responsibility of the co-operating agricultural chemical companies. In most cases, there is no problem and the use is registered as proposed. However, there are some occasions when the co-operating registrant will require that additional crop safety and/or product performance data to be developed. There are also occasions when the co-operating agricultural chemical company requires that additional safeguards against crop damage liability are included on the product label.

IR-4 conducts an average of 100 projects on food crops every year. Over 85% of these projects consist of residue studies. The remaining studies are designed to provide data to the registrants that the proposed use is safe and effective. This aspect of the IR-4 research plan comprises of nearly 700 field trials. In addition to the food program, IR-4 conducts over 600 ornamental efficacy and phytotoxicity trials and 40 plus Biopesticide Program projects.

Since 2000, over 80% of IR-4's research effort has involved new pest control technology with biopesticides and reduced risk chemistry. This huge shift from a defensive[1] programme to embracing new technology in a few short years was a direct result of the focus IR-4 placed on advocating this new technology. It was accomplished through a two-pronged approach consisting of partnering with the agricultural chemical companies and education of the minor crop stakeholders. IR-4 recognized that without access to the new technology it could not assist the minor crop growers. IR-4 solicited industry's willingness to work together on new product development strategies that, for the first time, included the minor crops in their development plans. The foundation for this close working relationship was the crop groups. With studies on a few key crops, many other minor crops were eligible for registration. The other aspect of IR-4's emphasis on new technology was the educational facet. It became clear that with reduced staffs in many of the companies due to mergers, those federal and state research/extension scientists were not always given the ability to test the new materials. IR-4 instituted a mechanism through publication of ***New Pest Control Products/Transition Solutions List*** to inform the public about the virtues of the new technology to assist in the transition away from FQPA [in full] vulnerable crop protection tools.

[1] During the late 1980's and early 1990's, IR-4 was very instrumental in developing a large body of residue data on existing products in order to maintain minor use registrations as part of the 1988 Amendments to the US Federal Insecticide Fungicide and Rodenticide Act reregistration program. IR-4's efforts supported about 700 minor uses on minor food crops

Since the IR-4 Project started in 1963, it has been responsible for residue data and other petitions to support over 6,500 food use clearances, more than 9,900 ornamental or non-food crop clearances and supported research on biopesticides that has resulted in over 300 biopesticide clearances. This is a tremendous accomplishment when measured against the level of funding and the efforts of the crop protection industry. The IR-4 supported clearances account for approximately 50% of all food use approvals granted by the EPA and for over 50% of the Agency's ornamental approvals.

MINOR USE CLEARANCE PROCESS IN CANADA

The problems that influence the availability of pest control products in the United States also affect the minor crop growers in Canada. However, it is generally recognized that the Canadian minor crop growers currently have access to fewer pest control products than their minor crop grower counterparts in the United States. To make matters worse, newer, safer (both from a human health and environmental point of view) pest control technologies for minor use crops are being approved in the United States at a much faster rate than in Canada. It is perceived that the Canadian regulatory process presents so many disincentives that many manufacturers of pest control products refrain from submitting applications.

Prior to June 2002, Health Canada's Pest Management Regulatory Agency (PMRA) essentially administered the minor use programme in Canada. There was a very small amount of research funding to directly develop data to support registration on minor crops. PMRA worked with the Canadian Horticulture Council to conduct studies for the most important projects. To assist with registering minor uses, PMRA utilized two regulatory tools to accomplish its task. Products that are already labeled in Canada on another major or minor crop are eligible for the User Requested Minor Use Label Expansion (URMULE) program. Agriculture and Agri-Food Canada (AAFC), grower organizations, crop specialists or other persons can sponsor URMULEs. Products that are not labelled in Canada currently but are available in the USA or Europe are eligible for the User Requested Minor Use Registration (URMUR) program. URMURs must be sponsored by the registrants of the active ingredient, supported by grower organizations, crop specialists and other industry personnel. All minor use proposals must be reviewed and approved by a representative from each Province that is assigned the responsibility of Providential?{Provincial} Minor Use Coordinators (PMUCs). The Pest Management Regulatory Agency empowered the PMUCs to serve as liaison between the PMRA and those who needed minor use materials.

Unfortunately, for many potential registrants, the URMUR/UMULE programmes are not working as expected. There are concerns that the programmes are not harmonized with US/OECD data requirements and usually require additional field-testing before registration of products is forthcoming. When additional testing was required, adequate funding was not available to conduct the tests.

In May and June 2002, the Government of Canada announced plans to provide significant resources to AAFC and PMRA to improve the availability of minor-use and reduced-risk products and help Canadian producers be less reliant on older active ingredients. The government, through various funding mechanism pledged approximately $16 million Canadian dollars annually to upgrade their research and regulatory capabilities. Agriculture and Agri-Food Canada will continue its work to help reduce chemical use through research and further

development of pest management systems that control pests using technologies such as crop rotation, cultivation, and biological control. The new funding will enable AAFC to create a programme similar to the IR-4 programme. Data generation trials and laboratory analysis will be conducted for minor-use pesticides of priority interest to Canadian growers and in conjunction with the IR-4 program. This will result in data being available for registration submissions at much the same time in both countries.

COLLABORATION BETWEEN THE UNITED STATES AND CANADA

Collaboration between the IR-4 Program and Canada has been occurring since 1996. Unfortunately due to limited funds, the Canadian Minor Use Program has only conducted approximately 90 field trials in co-operation with a limited number [of IR-4 magnitude of the residue studies.]?? The intent of this collaboration was to develop the appropriate data in the United States and Canada and concurrently submit the data to the respective pesticide regulatory agency. This collaboration was facilitated by the approval of the North America Free Trade Agreement (NAFTA) data zone map that allowed PMRA reviewers to mutually accept data from appropriate areas in the respective countries. In association with this research collaboration, PMRA completed its first IR-4 submitted work share petition with the U.S. EPA in 2002. PMRA and EPA both reviewed and accepted the data associated with the fungicide, fenhexamid on raspberry as acceptable to support registrations in both co-operating countries.

As noted previously, the Canadian government made a major funding commitment to minor crop growers in 2002 through PMRA and AAFC that will set up six Field Research Centers, three GLP Residue Laboratories and a Minor Use Center in addition to expanding the PMRA minor crop review capabilities including a Minor Use Team Leader. This commitment has allowed the Canada to expand their support of IR-4 projects to over 60 field residue trials in 2003 as part of the IR-4 prioritization program and should lead to more minor crop registration for both U.S. and Canadian minor crop growers, resulting in fewer trade issues. It is anticipated that the size of the collaborative programme will be even larger in 2004 and beyond.

The Render-4 Project – Start of the 4th stage of the EU review programme

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ABSTRACT

Defined by Regulation (EC) No 1112/2002, the Render-4* Project examined notifications for the remaining existing active substances to be reviewed in the 4th stage of the EU review programme. The evaluation for more than 200 active substances (e.g. attractants, plant extracts and micro-organisms) corresponding to 563 notifications was completed in May 2003. For more than 80 active substances and microorganisms either no notification or no admissible notification was submitted. As a result of the processing of the Render-4 Project these active substances are excluded from the review programme and will be withdrawn from the market in the Member States, by 31 December 2003.

INTRODUCTION

Following its experience with the Render-Project (3rd stage of the EU review programme for existing active substances), the European Commission has once again asked the Federal Biological Research Centre in Braunschweig (BBA) to take on the tasks defined in the Regulation. The aim of the Project was to prepare the 4th stage of the EU-review programme for active substances. Based on Regulation (EC) No 1112/2002 the Render-4 Project started with the notification procedure in July 2002. During the process, notifications for existing active substances were to be collected and evaluated. Active substances for which an admissible notification has been submitted will be completely reviewed in a succeeding programme.

For those active substances for which a commitment to further prepare the necessary dossier has been made, the time period referred to in Article 8(2) of Directive 91/414/EEC is extended until 31 December 2008, in order to allow for the submission of dossiers and the evaluation thereof.

LEGAL BASIS AND PROCESSING

Detailed rules for the implementation of the 4th stage of the work programme were laid down in Regulation (EC) No 1112/2002 which came into force on 1 August 2002. As defined in Annex V, the BBA (Render-4 Project) was the designated body processing and examining the notifications on behalf of the European Commission. The project was exclusively financed by notification fees. However, at the end of the project more than half of the paid fee was refunded to the notifiers.

* Review of EU Notifications under Directive 91/414/EEC and Related Regulations

The team began its work on 1 July 2002 and completed it on 31 August 2003 (Figure 1).

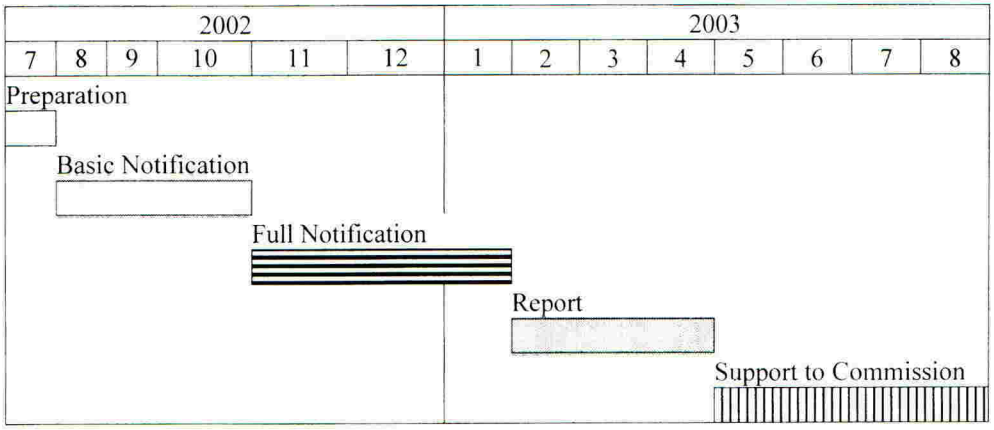

Figure 1. Project time frame and task blocks.

The Regulation provided a time schedule according to which the notification documents were to be submitted and evaluated. Evaluation reports had to be submitted to the Commission. The main focus was to advise and support notifiers in regard to the notification procedure, answer questions and solve problems dealing with the relevance and classification of some active substances. Ultimately, the team provided assistance to the Commission with completing further documents and regulations. Table 1 shows the most important dates and their points of reference in the Regulation.

Table 1. Dates and tasks of the Render-4 Project and their points of reference to Regulation (EC) No 1112/2002.

Date	Task	Regulation
01.07.2002	Project begin	
01.08.2002	Coming into force of the regulation	Article 9
31.10.2002	Deadline for submission of basic notifications	Article 4 (2)
31.10.2002	Deadline for full notifications (part 1)	Article 5 (2) (a)
31.12.2002	Commission report on notifications received	Article 6 (1)
31.01.2003	Deadline for full notifications (part 2)	Article 5 (2) (b)
31.01.2003	1st Render report on admissibility	Annex V (4)
31.03.2003	Deadline for notifications from Member States	Article 6 (2)
30.04.2003	2nd Render report on admissibility	Annex V (4)
30.04.2003	1st Commission report on admissibility	Article 6 (3)
31.07.2003	2nd Commission report on admissibility	Article 6 (3)
31.08.2003	Project end	

Similar to the procedure for the 3rd stage, all notification forms and a guidance document were provided as MS Word files and made available on the Internet or by e-mail. After completing the forms, the notifiers submitted the required documents electronically, e.g. by e-mail. The electronic form ensured a standard format, but was also designed to facilitate

completion and data transfer. The common use of standard software (MS Office) and the Internet, even by smaller companies, contributed to the success of this approach.

The vast amount of data required a database programme for effective evaluation. For this reason, an MS Access database was developed ("Renderix"), which was integrated into the Render-4 internal network. Use of this database supported the statistical approach and ensured an evaluation with a high degree of transparency and reproducibility.

ACTIVE SUBSTANCES AND REQUIREMENTS

The first group of approximately 160 active substances (listed in Annex I of the Regulation) covers the following categories of active substances:

- those authorised for use in human foodstuffs or animal feeding stuffs in accordance with EU-legislation,
- those which are plant extracts, animal products or derived thereof by simple processing
- those which are, or will be exclusively used as attractants or repellants (including pheromones), exclusively used in traps and/or dispensers, in conformity with Council Regulation (EC) No 2092/91 concerning organic farming.
- Disinfectants as specified in the Regulation

Notifications in this group mainly required limited information on the notifier and the identification of the active substance. In addition information on the mode of action, harmful organisms controlled and the nature of effect, had to be submitted. Most of them are used as plant growth regulators, insecticides or attractants. The following active substances being examples of this first group and used in more than 10 Member States:

- 1-Naphthylacetic acid
- Fatty acid potassium salt
- Iron-II-sulphate
- Paraffin oil
- Phoxim
- Pyrethrins
- Sulphur

The second group covers more than 50 active substances (listed in Annex II of the Regulation), which are:

- Micro-organisms including viruses.
- Active substances used as rodenticides.
- Active substances used on stored plants or plant products.

In addition to the data required for the first group the notifier had to submit a completeness check, the list of studies and the list of end points. The following relevant active substances and micro-organisms are used in more than 10 Member States:

- *Bacillus thuringiensis*
- Brodifacoum
- Bromadiolone
- Chlorophacinone
- Coumatetralyl
- Difenacoum
- Flocumafen

Some notified active substances were either not listed in the Regulation or did not fulfil the conditions of Directive 91/414/EEC or the Regulation. In such cases notifications were only included in the evaluation process if the notifier for example could prove that the active substance was definitely an existing one.

In some borderline cases the notifier had to be asked for further information on the mode of action or the intended uses in order to prove the relevance of the active substance. For example waxes and resins had to be excluded from the evaluation because they act by physical means only, and are therefore not active substances as defined by the Directive.
It was a difficult task to classify pheromones as plant protection products because this depends on their respective uses and related criteria (e.g. mating disruption, use as attractant, application with an insecticide). For substances used on stored plants, rodenticides or those applied as disinfectants additional explanations were required to ensure clear cut-off from their use as biocides in contrast to the plant protection use.

Unfortunately, some adjuvants or coformulants were notified by mistake and were consequently rejected or withdrawn. Finally some active substances were classified as new active substances and therefore not relevant for consideration in the 4th stage of the review programme (e.g. *Fusarium oxysporum*, *Coffea robusta*).

The notified active substances are predominantly repellants/attractants and insecticides to be applied in vegetables, ornamentals or orchards (Figure 2).

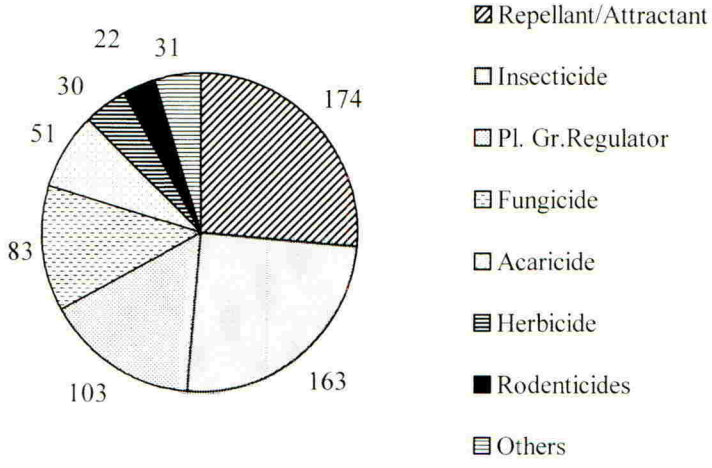

Figure 2. Functions of the notified active substances (multiple entries possible for one active substance).

The number of authorised active substances covered by the 4th stage is different in each Member State of the EU (Figure 3). Almost half of all notifications were submitted by notifiers based in the United Kingdom, France and Germany.

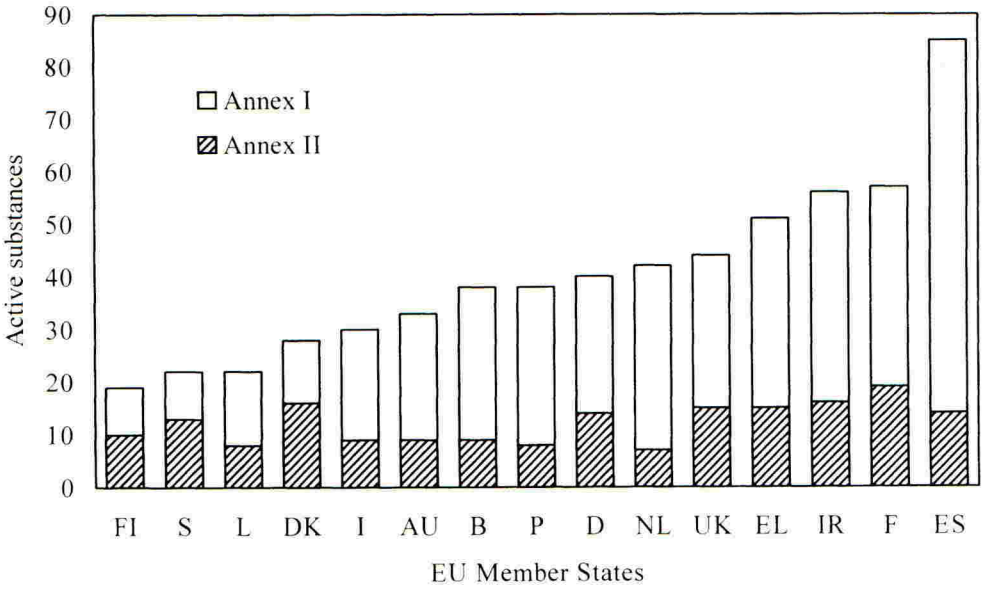

Figure 3. Number of authorised or used active substances of Annex I and II of Regulation (EC) No 1112/2002 in the Member States of the EU.

The aim of the project was not only to identify the active substances to be reviewed but also to select those notifications for which submission of a full dossier appears to be feasible and likely. The Regulation defined the criteria for admissibility of notifications including, completeness of the dossier currently available, list of end points, time limit, format and fee.

RESULTS AND CONCLUSIONS

After the evaluation process and consultation with the European Commission and experts of the Member States, 87 active substances and four species of micro-organisms had to be rejected and must be withdrawn from the market in the Member States of the EU by 31 December 2003 at the latest. Most of these active substances were not supported by the industry. Only very few were rejected because of the negative recommendation as a result of the evaluation process. Reason for rejection of these was basically that no use as a plant protection product could be identified. The following rejected substances are currently used in at least 3 Member States:

Boric acid
Calciferol
Coumachlor
Coumatetralyl
Difethialone
Flocumafen
Nitrogen
Propionic acid
Soyabean oil, epoxylated

However, most of the active substances to be withdrawn are obviously without great importance within the EU. This assumption is aided by the fact that only two Member States took the opportunity to notify after industry supported active substances had been published.

The deadline for the withdrawal of active substances might possibly be extended until 30 June 2007 if a Member State can claim an *essential use* for an active substance under specific conditions. For active substances of the 4th stage with a positive decision Member State authorisations can be prolonged until 31 December 2008.

The European Commission will take a formal decision on which active substances will be further evaluated under the 4th phase of the review programme, as announced in Article 6 (4) of Commission Regulation (EC) No 1112/2002. The date for submission of complete dossiers and identification of rapporteur Member States will be published in due course. In order to finalize the whole EU review programme on schedule by the end of 2008 dossiers should be requested in 2005 at the latest. However, at the moment the European Commission has not made a final decision on the data package required for the complete review of active substances of Annex I of the Regulation.

More information on the Render-4 Project is available on the Render-4 website hosted by the BBA (http://www.bba.de). Relevant documents can be found on the website of the European Commission (http://europa.eu.int/comm/food).

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EC (2002). *Commission Regulation (EC) No 1112/2002 of 20 June 2002 laying down the detailed rules for the implementation of the fourth stage of the work programme referred to in Article 8 (2) of Council Directive 91/414/EEC.*

EC (2002). Doc. *SANCO/3010/VI/91 of December 2002 listing active substances in plant protection products on the market on 25 July 1993 (Art. 4 of Council Directive 91/414/EEC) and their present authorisations in the Member States.*

EC (2003). *Doc. SANCO/10377/2003 of 24.06.2003 on the list of existing active substances and notifiers for which a notification in accordance with Article 5 of Commission Regulation (EC) No 1112/2002 has been assessed and appears to be admissible.*