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MONSANTO COMPANY

SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

vs.

MONSANTO COMPANY,

Defendant.

Case No. CGC-16-550128

Exhibit 1011, Part 2 of 2

AFFIDAVIT AND SWORN REPORT OF SYLVIA D. HALL-ELLIS, Ph.D.

Trial Date: June 18, 2018
Time: 9:30 a.m.
Department: 504

Exhibit 1011 – Part 2 of 2

Because there were no indications for a neurotoxic potential of glyphosate in acute and subchronic neurotoxicity studies and no evidence of neurological disturbances in pups in the multi-generation studies in rats, a developmental neurotoxicity study (DNT) is not needed.

Data with formulations/Published information

Over the last decade, several published studies investigated an association of glyphosate with neurotoxicity endpoints. In three papers, two human cases of Parkinson's disease were reported that became manifest not long after glyphosate exposure. The first case followed acute exposure to a glyphosate formulation while spraying a garden (Barbosa *et al.*, 2001, ASB2012-11557; da Costa *et al.*, 2003, ASB2012-11598). The second one occurred following chronic exposure of a factory worker in China (Wang *et al.*, 2011, ASB2012-12047) in a facility where a variety of pesticides including glyphosate were produced. However, a causal relationship of these (not quantified) exposures to glyphosate with Parkinson's disease is not likely. Occupational health surveillance did not provide evidence of a higher frequency of Parkinson's disease in glyphosate production workers. If the widely used glyphosate was in fact a causative agent of this fairly common disease, one would expect a significant number of cases associated with either acute and/or chronic exposures. Furthermore, occurrence of Parkinson's disease in survivors of acute intoxications following ingestion of high amounts of glyphosate products has not been documented.

While some epidemiological studies have indeed suggested statistical associations of Parkinson's disease with general pesticide exposure or insecticide or herbicide exposure (Engel *et al.*, 2001, ASB2012-11612), there is no evidence specifically for glyphosate. In the largest study to date, *i.e.*, the U.S. Agricultural Health Study, no association with reported glyphosate use was found (Kamel *et al.*, 2007, ASB2012-11862).
Human non-cancer epidemiologic outcomes related to glyphosate have been recently reviewed by Mink *et al.* (2011, ASB2012-11904), and there was no convincing evidence for an increased incidence of Parkinson's disease or other neurological disorders in individuals reporting glyphosate exposure.

A possible link with Parkinson's disease but also with other neurological diseases was examined in mechanistic studies in different systems such as *Caenorhabditis elegans* worms, in rats or cell cultures (Astiz *et al.*, 2009, ASB2012-11549; Negga *et al.,* 2011, ASB2012-11923; Gui *et al.* , 2012, ASB2012-11835). Sometimes, evidence for such links was reported but these findings are not considered relevant when the extremely huge database in laboratory animals with no evidence of neurotoxicity and the absence of suggestive epidemiological data in humans is taken into consideration.

Even though glyphosate (N-phosphonomethyl glycine) is sometimes allocated to the organophosphates, it is well known not to inhibit the activity of the cholinesterases. In line with that, in poisoning incidents in humans, common symptoms of acute acetylcholinesterase inhibition such as salivation, lacrimation, urination and defecation have not occured.
Cole *et al.* (2004, ASB2012-11594) evaluated 15 different pesticides for neurotoxic endpoints in *C. elegans* with analytical grade active ingredients, mostly noting reduced cholinesterase activities for pesticides causing neurotoxicity but not for glyphosate. Interestingly, the authors reported a low pH effect resulting in reduced cholinesterase activity in the high dose of glyphosate. However, glyphosate formulations contain the salts instead of the technical acid and, thus, do not have a low pH.

2.6.9 Summary of further toxicological studies

Mechanistic studies

Efforts were taken to elucidate the mechanism of salivary gland findings that were previously obtained in classical toxicological studies of different types in rats and occasionally in mice, *i.e.*, a higher organ weights and increased basophilic staining and enlargement of cytoplasm especially in the parotid salivary glands. By comparing the effects of high doses of citric acid and trisodium citrate dihydrate when given by gavage or in the diet, it became apparent that low pH conditions in oral cavity may result in similar effects mainly on the parotid salivary gland, perhaps due to local irritation ([redacted] 2010, ASB2012-11519). Acidic conditions may appear if a large amount of glyphosate is contained in the diet. Indeed, this effect should be considered rather adaptive than toxic but it will depend on its severity whether it should be regarded as potentially adverse.

[redacted] (1992, TOX9551954) found good evidence in F344 rats that an adrenergic mechanism may have also contributed to the salivary gland findings, at least at high dose levels when they fed 50000 ppm of glyphosate alone or in combination with exposure to either the adrenergic agonist isoproterenol or the antagonist propranolol or both.

Leaving mechanistic considerations aside, [redacted] (1996, ASB2012-11520 and ASB2012-11537) identified clear differences among rat strains with regard to their sensitivity to this type of effects. Administration of diets containing 20000 ppm glyphosate acid to male rats for 4 weeks resulted in an increase in parotid salivary gland weights in the F344 and AP (Alpk:AP$_f$SD, Wistar-derived) strains but not in CD rats. This increase proved reversible in AP rats after a 4-week recovery period whereas in F334 rats, there was still a difference to the controls. However, after 13 weeks on untreated diet, parotis gland weights were not different any longer. Microscopic examination of the salivary glands showed the most pronounced effect, again, in the F344 strain where there was diffuse cytoplasmic basophilia and enlargement of the parotid acinar cells. Similar but less pronounced effects occurred in the AP (Alpk:AP$_f$SD, Wistar-derived) and CD (Sprague-Dawley; Charles River) strains involving small foci of cells only. Complete recovery of histopathological changes was apparent in AP and CD strains following the 4-week recovery period. In the F344 strain, basophilia of parotid acinar cells was still to be seen in 5 out of 8 animals after a 13 week recovery period (control group: 1/8).

Although there is no evidence of necrosis, apoptosis or inflammation or that the cellular alterations would progress with time to preneoplastic or neoplastic lesions, the organ weight increase and histological alterations in salivary gland are considered clearly treatment-related. If exposure is sufficiently high, similar effects in man cannot be excluded. There is no reason to ignore these findings in risk assessment and at least if there is an increase in severity, they should be also taken into account for setting NOAELs/LOAELs in idividual studies.

Pharmacological activity of glyphosate was investigated *in vivo* in rats which received a single oral dose of 5000 mg/kg bw. One hour after dosing, no haematological, electrographic (ECG) or neurological (behavioural/functional) changes were observed when compared to control animals ([redacted] 1996, ASB2012-12054). When administered to isolated guinea pig ileum, glyphosate technical caused a contractile response similar to that seen with known parasympathomimetic agents. Results of exposure of isolated rat gastrocnemius muscle are reported above (see 2.6.7).

An immunotoxicity study in female mice did not provide evidence of suppression of humoral components of the immune system or effects on thymus and spleen weights after dietary administration of glyphosate at dose levels of up to 5000 ppm (*ca* 1450 mg/kg bw/day) over 28 days (Haas, 2012, ASB2012-11521).

Further studies were aimed to elucidate the mechanism of (acute) toxicity and to investigate possible additive effects. Experiments with i.p./i.v. administration to mice or rabbits revealed an impact of glyphosate ammonium salt on heart and respiratory functions as well as a decrese of the lethal dose under anesthesia (Takahashi and Kakinuma, 1992, TOX9552421). Irritation of the intestinal and stomach mucosa that might contribute to toxicity was shown by Mizuyama (1987, TOX9552430) in dogs and was more pronounced with a complete Roundup formulation than with glyphosate, its IPA salt or the surfactant that was contained. Bhide and Naik (1987, TOX9551964) reported an additive effect of glyphosate and 2,4- D and possibly also dalapon on mortality of rats after simultaneous administration of high doses.

Studies in farm animals

Following single or repeated adminstration of glyphosate acid and its IPA salt (MON0139) at high dose levels of more than 1000 mg/kg bw(/day) to farm animals (goats and cattle), the clinical picture of systemic intoxication in these animals was mainly characterised by gastrointestinal signs but also by depression, ataxia, convulsions, sternal recumbancy or head tremors. However, in spite of these neurological signs, gross pathological examination did not provide evidence of lesions in the nervous system and, therefore, histopathology of nervous tissue was not performed. In fact, histopathological examination identified the kidney as a target organ in ruminants and revealed mucosal irritation in the GIT (Rowe *et al.*, 1987, TOX9552422; 1987, TOX9552423; 1987, TOX9552424). In a study with repeated administration of a Roundup formulation (MON2139, containing 41.1% of the glyphosate IPA salt) to cattle over 7 days (Rowe *et al.*, 1987, ASB2010-8131), a NOAEL for systemic toxicity of 400 mg/kg bw/day was obtained. The LOAEL was 500 mg/kg bw/day and mortality was seen at 790 mg/kg bw/day (due to treatment-related aspiration pneumonia) and above. However, gastrointestinal signs predominated and neurological signs did not occur.
In sum, it is not likely that there is a specific neurotoxic potential of glyphosate in ruminants but it seems that systemic poisoning in these species may result in neurological signs. Based mainly on mortality and severity of clinical signs, ruminants appear a bit more sensitive to glyphosate effects than monogastric animals. Higher toxicity of certain formulations as compared to the active ingredient was confirmed once more.

Recently, a study has been published (Krüger *et al.*, 2013, ASB2013-11599) in which a large number of cows from eight Danish dairy farms (30 per farm) was investigated for glyphosate residues in the urine. All cows excreted glyphosate presumably because of residues in their feed (that was, however, not analysed for glyphosate) but the urinary concentrations in the individual dairy farms differed were very much with mean values from 10 to more than 103 µg/L. Based on these figures, a maximum daily intake of up to 16 mg glyphosate was calculated that may be compared to either the proposed ADI or to the NOAELs in toxicological studies in farm animals. Taking the first approach, calculated exposure would have been by 15 times lower than the ADI. A comparison to the NOAELs would give a wide margin of safety (approximately 1:4200). Thus, an impact on animal health is very unlikely. The authors claimed that alterations in some clinical chemistry parameters would have been linked to glyphosate but, on one hand, there is no proof that these findings were in fact adverse since clinical signs or pathological changes were not reported and, on the other, the statistical correlation was very poor. Furthermore, the origin and basis of reference values

were not given. A main deficiency of the study is the absence of a control group of cows with no glyphosate in their urines and proven absence of glyphosate in the diet.

Moreover, there is some discussion about possible effects of glyphosate on gut microflora for which evidence is mainly claimed because of *in vitro* results (e.g., Shehata *et al.*, ASB2013-8529). So far, a link of glyphosate residues in ruminants diet to a new disease in cattle that was mainly reported from Northern parts of Germany (Rodloff and Krüger, 2011, ASB2013-13311) has not been established and is not likely. Furthermore, there is no convincing proof that the observed clinical signs were indeed caused by *Clostridium botulinum* or its toxins as suspected by Krüger (2012, ASB2013-13312). However, because of the growing public concern about this disease especially in Germany and because an effect of glyphosate on micro-organisms due to inhibition of the enzyme EPSPS (that is common not only in plants but also in most bacteria and some other micro-organisms) cannot be excluded, the German Federal Institute for Risk Assessment (BfR) has commisioned a study by means of the "Rumen Simulation Technique" (RUSITEC). Its objective was to investigate wheter (1) quantitative composition of ruminal microflora or rumenal metabolism might be altered and (2) there is evidence of *C. botulinum* overgrowth. Two different experiments were performed (Riede *et al.*, 2013; ASB2013-14684). In the first one, the effects of a glyphosate-based herbicide (Plantaclean® XL; 360 g/l glyphosate, containing a tallowamine surfactant) on rumen fermentative parameters were studied. Total glyphosate doses per day were 0.26 or 2.31 mg per fermentation vessel. No major changes in rumen parameters were detected except slight decreases in NH_3-N-concentrations and increases in isovalerate production in response to the high dosage. There was an increase in (beneficial) *Bifidobacterium spp.* but the microbial community of *Clostridia* was not affected. In the second trial, no effects of the herbicide on growth of *C. sporogenes* (artificially added and used as a surrogate for *C. botulinum)* was found.

2.6.10 Summary of toxicological data on impurities and metabolites

2.6.10.1Aminomethyl phosphonic acid (AMPA)

Aminomethyl phosphonic acid (AMPA) is a major metabolite of glyphosate in soil and in genetically modified crops but was shown to occur only in traces in mammals (see 2.6.1). It is part of the residue definition for dietary risk assessment. AMPA was subject to comprehensive toxicological testing and can be currently regarded as one of the best known pesticide metabolites. It was of very low acute toxicity when adminstered to rats or mice via the oral and dermal routes and proved negative for skin sensitisation in Magnusson & Kligman tests.

Short-term toxicity was investigated in gavage/capsule and feeding studies in rats and dogs. Increased kidney weights in a subacute rat study (Heath *et al.*, 1993, TOX9300349) at 350 mg/kg bw/day and above were not confirmed in a 3-month study in the same laboratory under similar conditions up to the limit dose of 1000 mg/kg bw/day (Strutt *et al.*, 1993, TOX9300377). It is interesting to note that the specific histological lesions in salivary glands observed with glyphosate (see sub-sections above) were not confirmed by Heath *et al.* (1993, TOX9300349) for exposure to AMPA although these glands, including the parotis, were subject to careful examination. In a feeding study in rats (Estes *et al.*, 1979, TOX9552401), a decrease in body weight gain and food consumption, minor alterations in clinical chemisty parameters (increase in lactate dehydrogenase activity) and histological lesions (epithelial hyperplasia of bladder and renal pelvis) were observed at dose levels of 1200 mg/kg bw/day

and above that, in the whole, resembled effects of exposure to high doses of glyphosate. At an exaggerated dose level of 4800 mg/kg bw/day, there was some mortality (25 %) in female rats which died shortly after interim or final blood collections with death preceeded by gastrointestinal signs and general morbidity. The NOAEL in this study was 400 mg/kg bw/day.
In dogs, not effects of AMPA administration were noted and the NOAEL in a 3-month study was at least 263 mg/kg bw/day, *i.e.*, the highest dose tested ([redacted], 1991, TOX9552406).

AMPA was extensively tested for mutagenicity and proved consistently negative *in vitro* in bacteria (Ames test), in the mouse lymphoma assay and in rat hepatocytes (DNA damage and repair). *In vivo*, it did not produce an increae in micronucleus frequence in mouse bone marrow in two strains using either the oral or the i.p. route ([redacted] 1993, TOX9300379; [redacted] 1993, TOX9552413).

Developmental toxicity of AMPA was investigated in two studies in rats. [redacted] (1992, TOX9300348) did not detect any evidence of toxicity neither in the dams nor in the foetuses up to the limit dose of 1000 mg/kg bw/day. [redacted] (1991, TOX9552414) established a maternal NOAEL of 150 mg/kg bw/day because of the occurrence of clinical signs and a reduction in bw gain and food consumption at the upper dose levels of 400 and 1000 mg/kg bw/day. There was no evidence of teratogenicity but the mean foetal weight was lowered at the top dose level. Thus, the developmental NOAEL in this study was 400 mg/kg bw/day.

Taking all this data into consideration, it appears that AMPA is of equal toxicity as its parent compound. There is no specific or additional concern with this metabolite and the same reference values as for glyphosate should apply also for AMPA. Setting of an ARfD is not needed. Further studies (long-term, multigeneration, developmental toxicity in a second species) are not considered necessary.

2.6.10.2N-acetylglyphosate (NAG)

N-acetylglyphosate (NAG) is another important metabolite of glyphosate and is newly proposed to be part of the residue definition for monitoring and for dietary risk assessment. It will occur in certain genetically modified plants such as soy beans or maize following application of glyphosate and was evaluated by EFSA with regard to setting of import tolerances (EFSA, 2009, ASB2012-3480). For this purpose, a few toxicological studies had been submitted and were evaluated in 2008 by the RMS. This assessment resulted in the conclusion that NAG (and also N-acetyl AMPA that also may be formed) was of no higher toxicity than glyphosate and that, as for AMPA; the reference doses established for the parent compound, should also cover the. However, since this application scenario is beyond the scope of this re-evaluation of glyphosate in preparation of a decision on future approval in the EU, there is no need to report the studies with NAG in detail. Furthermore, the owner of these studies was not part of the GTF.

2.6.10.3Impurities

Definitive conclusions can be drawn only after a specification has been agreed and comparison of the different test materials to this specification is possible. From a toxicological point of view, it cannot be excluded that some of the very different high dose effects in the various toxicological studies with glyphosate (see above) are rather due to impurities than to the active ingredient. It was noted that test materials of different purity were applied and it can be reasonably assumed that their impurity profiles will also differ. Toxicological evaluation of specification and of relevance of impurities is included in Vol. 4.

2.6.11 Summary of medical data and information

Reports on medical surveillance on manufacturing plant personnel

Industrial hygiene air monitoring data for glyphosate from a Monsanto plant in Luling, Louisiana (U.S.A.) have been submitted for the years 1981-1998. Based on the measured low exposures to glyphosate in this manufacturing setting (well below the ADI) and because of low toxicological concern, glyphosate-specific medical monitoring was not considered necessary by Monsanto. No such data have been submitted from a Monsanto European manufacturing facility in Europe or by any of the other GTF member companies. Taking into account the large number of manufacturers and formulations, the RMS proposal is that such and perhaps more product-specific data on occupational exposures and occupational health surveillance of plant personnel should be requested on MS or zonal level for product authorisation.

Observations on exposure of the general population and epidemiological studies

Data on urinary excretion after occupational or presumably dietary exposure (Acquavella *et al.*, 2004, ASB2012-11528; Hoppe, 2013, ASB2013-8037) and the comparison of exposure estimates that may be calculated on this basis to the proposed reference values are reported under section 2.6.2 above.

A number of epidemiological studies of different types, extent and quality have been published in which exposure to glyphosate-based formulations in the studied populations was postulated. These publications adress either carcinogenicity, neurotoxicity or reproductive endpoints (fertility, occurrence of malformations) and, accordingly, are discussed in the respective sections of Volumes 1 (2.6) and 3.

Reports on clinical cases and poisoning incidents

For better understanding of the following, it must be emphasised that all the poisoning or irritation incidents resulted from exposure to glyphosate-containing plant protection products but not to the active ingredient. Thus, in principle, it is not possible to distinguish if they were due to the active substance or rather to co-formulants. From animal experiments, however, it is known that glyphosate acid was irritating to the eyes (*i.e.,* a sign that is frequently associated also with mucosal irritation) but of low toxicity *via* all relevant routes. Even eye irritation was less pronounced in studies with glyphosate salts as compared to the acid. These salts are used for formulation of commercial products. Accordingly, one might assume that (frequently irritant or even corrosive) co-formulants will have contributed the most to intoxications following systemic intake and perhaps also to the irritation in cases of eye contact with glyphosate-based herbicides.

The extensive and still increasing use of glyphosate as an active ingredient in herbicides worldwide, rather than the (low) toxicity of this compound, may explain the relatively large number of poisoning incidents that happened and was published. Extensive reviews of clinical cases were published by Bradberry *et al.* (2004, ASB2012-11576) and by Lee *et al.* (2008, ASB2012-11879).

In some countries, poisoning incidents due to plant protection products are reported to the regulatory agencies but this knowledge is often either not made public or not shared with authorities in other countries. Thus, apart from what was published in the open literature, the RMS was aware only of data collected in Germany and, to some extent, in Brazil.
Burger *et al.* (2009, ASB2013-11831) briefly summarised a total of 60 reports by physicians from Germany to the Federal Institute for Risk Assessment on cases of poisoning with glyphosate herbicides since 1990. In the vast majority of 52 cases, only slight health impairment was reported. In four cases, health disturbances were considered "moderate" whereas the only one actually life-threatening case was the result of ingestion of 200 mL of a herbicide containing glyphosate and a tallowamine surfactant with suicidal intent. In the three remaining cases, no symptoms were reported or their severity could not be evaluated.
More than 650 cases of intoxication/irritation ascribed to ingestion of/contact to glyphosate-based herbicides are mentioned in an overview on poisoning incidents from Brazil that was kindly provided to the RMS by the Brazilian National Health Surveillance Agency (ANVISA, 2012, ASB2013-13413). This data was collected between 2010 and 2012 in some federal states but it is not clear if it is representative for the whole huge country in which the agricultural conditions in general and also those of pesticide use are extremely different. At the first glance, the exposure routes, ingested amounts, circumstances (accident, suicidal attempt), clinical signs and medical treatment are similar to what is known from Germany and from the literature. The much higher total number of cases seems to reflect the applied amount of glyphosate and its formulations that is by orders of magnitude higher in Brazil than in Europe. However, further analysis is considered necessary before these data can be used for risk assessment purposes.

What is known on the course of clinical cases, signs and symptoms is summarised below and presented in greater detail in Volume 3.

Clinical signs and symptoms of poisoning – skin and eye contact
The vast majority of reported clinical signs following exposures (apart from attempted suicides or rare accidents) comprise skin and/or eye irritation or irritation of the respiratory tract by inhalation of spray mist.
Contact with skin may produce a dermatitis similar to that caused by detergents (Bradberry *et al.*, 2004, ASB2012-11576) although the active ingredient was not irritating to the skin in laboratory animals.
Phototoxic reactions [sunlight or ultraviolet (UV) light induced skin reactions] have been reported. This was believed to be due to an antimicrobial additive (benzisothiazolone) which is present in certain residential use (*i.e.,* non-agricultural) products containing 10 % glyphosate or less (Bradberry *et al.*, 2004, ASB2012-11576).
Eye exposures have generally resulted in temporary conjunctival irritation, clearing either after irrigation or within 1-2 days. A review of ocular exposures to US glyphosate-surfactant formulations (1513 exposures over a 5-year period), showed no permanent eye injury (Acquavella *et al.*, 1999, TOX2002-699; Bradberry *et al.,* 2004, ASB2012-11576). Eye contact is not expected to cause systemic effects or serious ocular injury.

Clinical signs and symptoms of poisoning – Oral intake
Ingestions of more than approximately 50 mL ("one mouthful", if real amount unknown) of a product with >10 % glyphosate concentration may be clinically significant. In contrast, glyphosate concentrations of less than 10% have rarely if ever produced toxicity. Most serious illness was observed following ingestion of the 41% (glyphosate IPA salt) concentrate. In the absence of extensive clinical experience for the 11-40% concentration

range, any ingestion of more than 50 ml of a preparation with greater than 10% glyphosate salts should be considered as a potential cause for the subsequently described symptoms.

Minor gastrointestinal exposures are likely to be asymptomatic but the patient may experience an unpleasant taste, tingling, mild self-limiting nausea and vomiting. Self-limiting diarrhoea may also occur.
After significant exposures, a burning sensation in the mouth and throat, salivation, oral erythema, sore throat, dysphonia, dysphagia, epigastric pain, nausea, spontaneous vomiting, abdominal pain and diarrhoea are common and may last up to a week.
Serum amylase may be elevated and isoenzyme analysis done in a few cases identified a salivary gland origin (Tominack *et al.*, 1989, TOX9552426).

Hypotension is common after ingestion of a mouthful or more of the concentrated product (not the diluted forms) and will usually favourably respond to intravenous administration of fluids and pressor amines. If not responsive to this treatment, however, hypovolemic shock may result in oliguria, anuria, organic failure and ultimately in death.
Severe or prolonged vomiting and diarrhoea may induce fluid and electrolyte imbalance.
Tachypnea, dyspnea, cough and bronchospasm including cyanosis have been seen in severe ingestions. Transient hypertension may also occur. In laboratory analysis, abrupt rises in BUN and serum creatinine may be seen. Hemoconcentration can result result from intravascular volume depletion and could possibly indicate severe capillary fluid leakage (Tominack *et al.*, 1989, TOX9552426; Bradberry *et al.*, 2004, ASB2012-11576).

Several case reports indicate clinically significant hyperkalemia following ingestion of large amounts of glyphosate-potassium salt concentrate solutions (Bando *et al.,* 2010, ASB2012-11556; Kamijo *et al.*, 2012, ASB2012-11863).

Metabolic acidosis is often seen in a severely poisoned patient (Bradberry *et al.,* 2004, ASB2012-11576) and may fail to respond to bicarbonate therapy. Although the exact etiology is unknown, a lactic acidosis is suspected.

There have been no reports of primary convulsions after ingestion and most patients are present with a clear sensorium unless another substance, such as alcohol, has been co-ingested or severe hypoxemia has occurred (Tominack *et al.*, 1989, TOX9552426). However, in other cases, "moderate disorders of consciousness" have been reported within 48 hours after ingestions of the concentrate with suicidal intention (Sawada and Nagai 1987, Z35531; Sawada *et al.,* 1988, Z35532).

Aspiration pneumonia, pulmonary oedema and respiratory failure have been seen although the exact role of aspiration has not been fully investigated.

Mild fever may occur even in the absence of infection. In addition, leukocytosis without evidence of bacterial infection has been noted in peripheral blood after ingestion of the concentrate (Bradberry *et al.*, 2004, ASB2012-11576).

No direct hepatotoxic effects have been noted; however, minor elevations in transaminases and bilirubin were reported (Tominack *et al.*, 1989, TOX9552426; Bradberry *et al.*, 2004, ASB2012-11576).

Respiratory distress requiring intubation, pulmonary oedema, shock (systolic BP < 90 mm Hg), altered consciousness, abnormal chest X-ray, ingestion of over 200 cc concentrate (41 %), or renal failure making dialysis necessary have been associated with a higher risk of poor clinical outcomes including mortality (Lee *et al.*, 2000, ASB2012-11512). These authors also developed a prognostic index based upon these factors. However, as onset of symptoms may be delayed, early use of such prognostic indicators and too much reliance on them may lead to an under-estimate of clinical severity.

Clinical signs and symptoms of poisoning – Inhalation

An isolated case report from Israel suggests the development of acute pneumonitis in a worker (smoker) shortly after he had repaird a spraying device (not in operation). From "occupational history", the occupational physicians concluded that he had been exposed to Roundup herbicde and suspected a polyoxyethylene amine surfactant in the product as the possibly responsible agent (Pushnoy *et al.,* 1998, ASB2012-11513). However, actual exposure and its extent could not be really substantiated in this case. Accordingly, the occurrence of pneumonitis in this individual is more likely to be coincidental by nature although a (different) occupational origin seems plausible (Goldstein *et al.*, 1999, ASB2012-11511).

However, Burger *et al.* (2009, ASB2013-11831) also reported severe acute dyspnoe, rise in body temperature and histological lung changes (acute alveolitis and bronchiolitis) in a 59 years old German farmer who had sprayed a herbicide containing glyphosate on a warm day for three hours without respiratory protection. First clinical symptoms occurred seven hours after spraying. The patient was given i.v. steroids at high doses and antibiotic cover. This therapy was successful but six months later, he still complained of moderate breathing difficulties under conditions of exercise. It was suspected that the combination of glyphosate with the tallowamine surfactant in the formulation might have caused this incident.
In addition, in the same reference, 20 cases of inhalative exposure among a total of 60 reports on confirmed or presumed poisoning incidents with glyphosate herbicides from Germany (since 1990) were mentioned with breathing difficulties occurring in 50 % of the affected people. No more details on clinical courses or outcomes were given but it was emphasised by the authors as "striking" that the involved products nearly always contained tallowamines.

Thus, intoxications following inhalative exposure to glyphosate-based products may occur and it seems reasonable to assume that tallowamine surfactants might have played the crucial role in such incidents.

First aid measures and therapeutic regimes

First aid measures and therapeutic regimes have been proposed by the notifiers and may be found in Volume 3 but were not evaluated by RMS toxicologists.

Expected effects and duration of poisoning as a function of the route, extent and duration of exposure

The expected effects of acute exposures reflect the clinical experience as desribed above and may be summarised as follows:.

- Skin irritation following exposure to glyphosate-based herbicides is mostly due to surfactants and will be generally limited to topical irritation which will resolve within 3 days to 1 week following exposure. If exposure is aggravated by occluded

conditions or physical abrasion, more severe skin injury with open skin injury may result and may take longer to fully resolve.

- Eye irritation will generally resolve within 3-7 days of exposure. Most irritation is minor but exposure to concentrate or the occurrence of a foreign body or of abrasions (from rubbing the eye) may result in corneal abrasion requiring topical antimicrobial therapy, often occurring in conjunction with topical corticosteroids and temporary eye patching to provide symptomatic relief. As noted above, a large study of ocular exposures to glyphosate-surfactant products in the U.S. demonstrated no long term eye injury.

- Following minor or incidental ingestions, or ingestion of fully diluted formulations, gastrointestinal upset with nausea, vomiting, and diarrhoea may occur. Nausea and vomiting usually resolve within a few hours of ingestion. Diarrhoea may last for several days but is generally not severe. Following ingestion of a larger amount, the onset of systemic symptoms may be delayed by several hours. For serious ingestions having major electrolyte disturbances or life threatening alterations of cardiovascular performance, medical intervention may be life saving. Fatalities due to cardiovascular failure are generally delayed by 12 – 36 hours. For serious but non-fatal cases, primary clinical injury generally is manifest within 72 hours but secondary complications such as infection or respiratory distress syndrome may supervene. The majority of serious but surviving cases will fully recover within 7-10 days of ingestion. Individuals with complicate clinical courses can require a more extended and highly variable time to recover.

- Glyphosate products do not contain readily volatile ingredients and thus inhalation exposure will be limited to droplets, which will deposit primarily in the upper airways. Resulting irritant symptoms such as breathing difficulties, most likely due to surfactants, will generally resolve within hours to a few days following exposure. In rare cases, treatment for lung symptoms might become necessary.

Short- or long-term effects in consumers due to dietary exposure to glyphosate via residues are not to be expected when the whole toxicological profile of this active ingredient is taken into account and in particular when the wide margin between the exposure and the high dose levels causing adverse effects in laboratory animals is considered.

2.6.12 Toxicological end point for assessment of risk following long-term dietary exposure - ADI

In general, the "Acceptable Daily Intake" (ADI) is based on the highest dose at which no adverse effect was observed in the most appropriate study in the most sensitive laboratory animal species. In case of glyphosate, this approach must be modified, simply because of the fact that most toxicological endpoints are covered by a number of studies from different notifiers but of the same quality. For most toxicological endpoints, it is not possible to rely mainly on one particular study and to leave the other studies either aside or to consider them as supportive or confirmative only. Instead, it is more appropriate to establish "overall" NOAELs/LOAELs for the areas of toxicological testing and for the different species, based on all valid studies that were submitted to adress this particular endpoint. It is acknowledged that separate assessment of the studies that were submitted by one or the other applicant might

have resulted in different proposals for the reference doses but this approach cannot be taken and all available information must be taken together into consideration.

The same principle was followed in the previous EU evaluation resulting in the inclusion of glyphosate into Annex I of Directive 91/414/EEC (EU, 2001, ASB2009-4191). The ADI of 0.3 mg/kg bw was established on the basis of all long-term studies in rats which were available at that time.

In general, long-term studies are often the most suitable for deriving the ADI, in particular for a substance of that low acute and short-term toxicity as glyphosate. Based on the six combined chronic toxicity/carcinogenicity studies that were now considered valid by the RMS either upon first assessment or during re-evaluation (see Table 2.6–16), an "overall NOAEL" in the magnitude of 100 mg/kg bw/day appears reasonable. This is a higher figure than established before (EU, 2001, ASB2009-4191) because for the previous evaluation, in line with former regulatory practice, the NOELs (see Table 2.6–7a) instead of the NOAELs had been used. In addition, an additional study by [redacted] (1981, TOX2000-595) was included that is now considered not acceptable any longer and in which no effects had occurred up to the highest dose level of 31 mg/kg bw/day.

Table 2.6-16: High quality combined chronic toxicity/carcinogenicity studies in rats forming the basis for EU evaluation of this endpoint

Study	Owner	NOAEL	LOAEL	Overall assessment
[redacted] 2009 ASB2012-11490	Nufarm	285 mg/kg bw/d	1230 mg/kg bw/d	Not carcinogenic; high dose effects on bw gain, bone marrow, clinical chemistry, skin
[redacted] 2001 ASB2012-11488	Syngenta	361 mg/kg bw/d	1214 mg/kg bw/d	Not carcinogenic; high dose effects on bw and food consumption, clinical chemistry, kidney, prostate
[redacted] 1997 ASB2012-11484, ASB2012-11485 ASB2012-11486, ASB2012-11487	Arysta	104 mg/kg bw/d	354 mg/kg bw/d	Not carcinogenic; high dose effects on bw and food consumption, caecum, skin
[redacted] 1996 TOX9651587	Feinchemie	60 mg/kg bw/d	595 mg/kg bw/d	Not carcinogenic; high dose effects on eyes (cataracts) and clinical chemistry
[redacted] 1993 TOX9750499	Cheminova	100 mg/kg bw/d	300 mg/kg bw/d	Not carcinogenic; high dose effects on bw gain, liver, salivary glands
[redacted] 1990 TOX9300244	Monsanto	89 mg/kg bw/d	362 mg/kg bw/d	Not carcinogenic; high dose effects on stomach mucosa (irritation), bw, liver, eyes (cataracts)

This "overall NOAEL" is further supported by the chronic (one-year) study in rats by Milburn (1996, TOX2000-1998) in which the NOAEL was 141 mg/kg bw/day. It is below the NOAELs that were established for long-term toxicity in the mouse (150 mg/kg bw/day; based on [redacted] 2001 (ASB2012-11491), [redacted] 1997 (ASB2012-11493), and [redacted] 1983, TOX9552381), the multigeneration studies in the rat (lowest value for parental and offspring toxicity 197 mg/kg bw/day; [redacted] 1992, TOX9552389) or in the one-year studies in the dog (overall 300 mg/kg bw/day; [redacted] 1990 (TOX9552384) and

[redacted] 1997, ASB2012-11458), *i.e.*, in the studies that are usually also taken into account for ADI setting.

When the usual assessment factor of 100 is used (and there is no apparent reason to select another one), an ADI of 1 mg/kg bw would result. This value is numerically the same as that one established by WHO/FAO (JMPR, 2004, ASB2008-6266), based on the 2-year rat study by [redacted] (1993, TOX9750499) for which the same NOAEL of 100 mg/kg bw/day was derived as by the RMS in the current EU re-evaluation.

However, since it is also a widely accepted requirement and general practice to look at the most sensitive species, the developmental studies in the rabbit must not be ignored.

At the same dose level of 100 mg/kg bw/day that caused no effects in long-term feeding studies in rats, there were several deaths in pregnant rabbits in the study by [redacted] (1993, TOX9551106) that must be considered treatment-related. In the studies by [redacted] *al.* (1980, TOX9552392), [redacted] (1991, TOX9552393), [redacted] (1996, ASB2012-11499) and [redacted] (1996, TOX2000-2001), the maternal LOAELs were in the magnitude of 150 to 200 mg/kg bw/day. Even though the effects were not that severe as observed by [redacted] (1993, TOX9551106) and mortality at these dose levels was only occasionally seen ([redacted] 1980, TOX9552392), these LOAELs were much lower than in any other type of studies with glyphosate. A particular vulnerability of the (pregnant) rabbit was further confirmed by the high mortality rate in the study by [redacted] (1980, TOX9552392) at 350 mg/kg bw/day as well as by abortion and one death reported at the top dose level of 300 mg/kg bw/day in the study of [redacted] (1995, ASB2012-11498).

In addition, first developmental effects in rabbits (mainly post-implantation losses) were observed at a dose level of 200 mg/kg bw/day ([redacted] 1996, ASB2012-11499).

Based on all the latter considerations, it seems most appropriate to derive the ADI from the NOAEL for both maternal and developmental toxicity of 50 mg/kg bw/day as established independently by [redacted] (1991, TOX9552393) and [redacted] (1996, ASB2012-11499). In fact, a lower maternal NOAEL of 20 mg/kg bw/day was found in the study by [redacted] (1993, TOX9551106) but it is in no way mandatory and not usual to use the lowest available value if there is evidence that it results mainly from dose spacing. The proposed figure of 50 mg/kg bw/day is well below the LOAEL of 100 mg/kg bw/day in the study by [redacted] (1993, TOX9551106). In contrast, for the maternal NOAEL of 75 mg/kg bw/day in the study by [redacted] (1980, TOX9552392), the margin to a dose causing maternal death in another experiment (100 mg/kg bw/d according to [redacted] 1993, TOX9551106) might be too small.

If 50 mg/kg bw/day is accepted as point of departure, the resulting **ADI** for glyphosate is **0.5 mg/kg bw.**

This reference dose as proposed by the RMS is slightly higher than the previously established value in the EU of 0.3 mg/kg bw and by 50 % lower than the ADI that was set by JMPR (2004, ASB2008-6266). However, it must be emphasised that the database that was available for the WHO/FAO evaluation did not contain many of the studies that have been considered for this EU review. Thus, only two of the developmental studies in rabbits ([redacted] 1991, TOX9552393 and [redacted] 1996, TOX2000-2001) were evaluated by JMPR in 2004.

The notifiers, *i.e.,* the GTF, had proposed a markedly higher ADI of 3 mg/kg bw, derived from the NOAEL in the long-term rat study by [redacted] (1993, TOX9750499) which had been set at 300 mg/kg bw/day, in contrast to evaluation by the RMS.

2.6.13 Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)

A low acute oral toxicity of glyphosate was proven in a huge number of studies. In an acute neurotoxicity study, the NOAEL for systemic effects was 1000 mg/kg bw (*i.e.* the limit dose that might justify a need for an ARfD) and there was no evidence of neurotoxicity. There is no evidence that adverse effects in repeated dose studies, including developmental studies in rats or rabbits, might result from a single oral exposure or would occur within the first days of treatment.. Accordingly, **no ARfD** is needed.
The notifiers have also not suggested an ARfD. The same approach has been taken by the WHO/FAO in its 2004 evaluation (JMPR, 2004, ASB2008-6266).

2.6.14 Toxicological end point for assessment of occupational and bystander risks – AOEL

For AOEL setting, usually a suitable NOAEL from one of the so-called "mid-term" studies is chosen to reflect the expected length of operator exposure. This selection of studies comprises the 90-day studies in rodents and dogs and, if available, the one-year dog study, subchronic neurotoxicity, the reproduction (one- or two-generation) and developmental studies. In case of glyphosate, this is a huge database that is summarised in Table 2.6–17.

Table 2.6-17: Studies to be taken into account for deriving a systemic AOEL for glyphosate

Study type/endpoint	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d)	References
90 d, subchronic, rat	300 … 414 (overall)	569 (lowest)	[redacted] (1991, TOX9552364) [redacted] (1993, TOX9650149) [redacted] (1996, TOX2000-1990) for NOAEL; [redacted] (1995, ASB2012-11452) for LOAEL
90-d, subchronic, mouse	500 (lowest)	1065 (lowest)	[redacted] (1992, TOX9551954)
90 d, subchronic, dog	300 (overall)	1000 (lowest)	[redacted] (1996, TOX2000-1991), [redacted] (1999, ASB2012-11455) and [redacted] (2007, ASB2012-11454)
1-yr, subchronic, dog	300 – 500 (overall)	926 (lowest)	[redacted] (1990, TOX9552384), [redacted] (1996, TOX2000-1992), [redacted] (2007, ASB2012-11457)
Subchronic neurotoxi-city, rat	617 (systemic effects)	1546 (systemic effects)	[redacted] (1996, ASB2012-11501)
Reproduction, rat	Parental: 300-400	Parental: 985 (lowest)	[redacted] (1997 [redacted]

	(overall) Reproductive: 351 (lowest) Offspring: 300-400 (overall)	Reproductive: about 1000 (lowest) Offspring: 985 (lowest)	ASB2012-11495), [redacted] (2000, TOX2000-2000), [redacted] (2007, ASB2012-11494)
Developmental toxicity, rat	Maternal: 300 (lowest) Developmental: 300 (lowest)	Maternal: 1000 (lowest) Developmental: 1000 (lowest)	[redacted] (1991, TOX9552393), [redacted] (1995, ASB2012-11497)
Developmental toxicity, rabbit	Maternal: 50 (overall) Developmental: 50 (lowest)	Maternal: 100 (lowest) Developmental: 200 (lowest)	[redacted] (1991, TOX9552393), [redacted] *al,* (1993, TOX9551106), [redacted] (1996, ASB2012-11499)

The rabbit appeared the most sensitive species providing the lowest NOAELs and LOAELs with the most serious effects among all species at relatively low dose levels.
Based on the same considerations as for the ADI, the AOEL should be derived from the NOAEL of 50 mg/kg bw/day for maternal and developmental toxicity in the rabbit ([redacted] *et al.*, 1991 (TOX9552393); [redacted] 1996, ASB2012-11499), supported by [redacted] (1993, TOX9551106) and [redacted] (1980, TOX9552390). The maternal NOAEL of 75 mg/kg bw/day in the latter study had been used as the basis for AOEL setting during the previous EU evaluation (DAR, 1998, ASB2010-10302). Using the safety factor of 100 and the previous assumption of 30 % oral absorption, a numeric value of 0.2 mg/kg bw/day was calculated.

The safety factor of 100 should be maintained but oral absorption is now assumed to be as low as 20 % (see 2.6.1). If 50 mg/kg bw/day is used as the suitable point of departure [because the NOAEL in the study by [redacted] (1980, TOX9552390), was to close to a dose causing maternal deaths in another study in rabbits] the resulting **AOEL** is **0.1 mg/kg bw/day**.

The GTF had proposed a different systemic AOEL that was by 12 times higher. The suggested numeric value of 1.2 mg/kg bw/day was based on the 90-day rat study by [redacted] (1996, TOX2000-1990) in which the NOAEL was 414 mg/kg bw/day. This NOAEL was agreed with by the RMS but it is higher than the overall NOAELs for both maternal and developmental toxicity in the rat and, in particular, does not take into consideration the developmental studies in rabbits. The latter studies were not used because it was argued that the effects were due to gavage administration of a low pH organic acid causing mucosal irritation in the gut to which the rabbit is particularly sensitive. However, it was not proven that the effects were local by nature and also the low pH is an inherent property of glyphosate that might produce adverse effects.
Numerically, the proposed NOAEL was also slightly higher than the (overall) NOAEL for subchronic toxicity in the dog and the NOAELs for parental, offspring and reproductive toxicity as obtained in two-generation studies in rats.
Furthermore, the GTF used the previous assumption of 30% oral absorption for correction of the systemic AOEL instead of 20% as it is proposed now by the RMS.

Apparently, there is no reason to derive separate dermal or inhalative AOELs.

2.6.15 Summary of product exposure and risk assessment

MON 52276 exhibits low acute oral, dermal and inhalation toxicity, is slightly irritant to skin, slightly to moderately irritant to eyes and is not a skin sensitiser. No additional classification has to be adopted for MON 52276 due to known toxicological properties of the active substance or any of the co-formulants.
For a short summary see Table 2.6–18 and Table 2.6–19 below.

Table 2.6-18: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for MON 52276 by the RMS

Type of test, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Dir. 67/548/EEC)	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat (OECD 401)	> 5000 mg/kg bw	Yes	None	None	[redacted] 1991 TOX9552438
LD_{50} dermal, rat (OECD 402)	> 5000 mg/kg bw	Yes	None	None	[redacted] 1991 TOX9552439
LC_{50} inhalation, rat	Not submitted, not necessary. Justification presented in Vol. 3, B.6.11)				
Skin irritation, rabbit (OECD 404)	Non-irritant	Yes	None	None	[redacted] 1991 TOX9552440
Eye irritation, rabbit (OECD 405)	Non-irritant	Yes	None	None	[redacted] 1992 TOX9552441
Skin sensitisation, guinea pig (OECD 406, Buehler (9 applications)	Non-sensitising	Yes	None	None	[redacted] 2001 TOX2005-1135
Supplementary studies for combinations of plant protection products	No data – not required				

Table 2.6-19: Additional toxicological information relevant for classification/ labelling of MON 52276

	Substance (Concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Dir. 67/548/EEC and/or in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Dir. 67/548/EEC, in Dir. 1999/45/EC and/or in Reg. 1272/2008)

Toxicological properties of active substance (relevant for classification of product)	None			
Toxicological properties of non-active substances (relevant for classification of product)	None			
Further toxicological information	No data – not required			

Dermal absorption of glyphosate in the representative formulation MON 52276 was very low. In the high, mid and low concentrations, absorption rates of 0.1, 0.2, and 0.3 % were obtained in an *in vitro* experiment with 24-hour exposure on human epidermis (Ward, 2010, ASB2012-5383). The suitable figures from above were used for exposure calculations and risk assessment.

MON 52276 is a herbicide used for foliar spray application in various crops outdoors. The maximum recommended application rate is 3 x max. 2.88 kg a.s./ha (maximum dose per season not to be exceeded 4.32 kg a.s./ha) in orchard crops, vine etc. or 2 x 2.16 kg a.s./ha in crops treated with tractor-mounted ground boom sprayers such as cereals etc.. The estimated operator exposure according to the German model does not exceed the AOEL of 0.1 mg/kg bw/day without PPE. In the case of using knapsack sprayers in orchard crops etc. estimated operator exposure according to the UK POEM accounts for 207 % of the AOEL without PPE, so that gloves during mixing/loading and application as well as an impermeable coverall during application are necessary (85 % of AOEL). On the other hand, no PPE is needed according to the UK POEM for crops treated using tractor-mounted ground boom sprayers (76 % of AOEL).

Predicted worker exposure does not exceed the AOEL either. Even for prolonged inspection or maintenance tasks of 8 hours the AOEL is exploited with 8.6 % without PPE.

Estimated bystander and resident exposure is below the AOEL even if direct applications on pasture or lawn are considered for residents (bystanders: adults 1.35 %, children 1.33 % of AOEL; residents: adults 1.85 %, children: 16 % of AOEL).

Remarks on surfactants included into glyphosate-containing plant protection products

All glyphosate-containing plant protection products contain surfactants or - if not present as an integral component – are to be mixed with surfactants as a compulsory additive to produce the ready-to-use dilution. As has already been discussed during the first Annex I inclusion procedure for glyphosate it became apparent that glyphosate-containing products were more toxic than glyphosate alone. This phenomenon was attributed predominantly to the presence of particular surfactants, namely the POE-tallowamines.
Some MS may wish to allow for this in the context of the national risk assessment for POE-tallowamine containing glyphosate formulations. Therefore, a toxicological evaluation of POE-tallowamines (including reference values) is provided in a separate paragraph within Vol. 3 (B.6.13.3) of this RAR.

MON 52276 which is the representative formulation here **does not** contain any POE-tallowamines.
Instead, a different type of surfactant, i.e. a quarternary ammonium compound, is used for MON 52276.
Since studies on MON 52276 concerning acute toxicity, skin and eye irritation as well as skin sensitisation were performed with the original preparation of MON 52276 the results for these toxicological short-term endpoints also reflect possible effects provoked by the surfactant. No further studies are needed according to the data requirements for plant protection products. Therefore, no toxicological long-term studies were submitted using the formulated product or the surfactant alone. Moreover, up to now no reference values have been considered necessary for the surfactant used, thus, no respective risk assessment was required.
According to the material safety data sheet for the surfactant provided by the applicants this co-formulant was not mutagenic in an Ames-test. No further information on toxicological long-term endpoints was given in this material safety data sheet.

In addition, MON 52276 has been authorised within the EU for many years. There are no medical data which have been collected by occupational physicians or poisoning emergency centres describing long-term adverse health effects for operators provoked by this plant protection product until today.

2.7 Residues

2.7.1 Summary of storage stability of residues

The storage stability of glyphosate and AMPA was investigated in all matrix groups. For N-acetyl-glyphosate and N-acetly-AMPA only high water content, high oil content, high starch content and other plant matrices were investigated. The following intervals were identified without a significant decline of the residue (>70 % remaining):

Glyphosate

High acid content matrices (oranges; tomatoes)	>14 to >31 months
High water content matrices (clover; maize forage, green plant and stover; soya bean forage; sorghum stover; sugar beet roots and leaves)	>9 to 31 months
High oil content matrices (linseeed; rape seed; soya beans)	>18 to >24 months
High starch content matrices (barley, maize, rye, sorghum and wheat grain)	18 to >48 months
High protein content matrices (beans, dry)	>18 months
Other plant matrices (barley, rye, soya bean and wheat straw; soya bean hay)	18 to >45 months
Animal commodities (fat, muscle, liver and kidney from swine, cattle and poultry; milk; eggs)	14 to >26 months

AMPA

High acid content matrices (oranges; tomatoes)	>14 to >31 months
High water content matrices (clover; maize forage, green plant and stover; soya bean forage; sorghum stover; sugar beet roots and leaves)	6 to 24 months
High oil content matrices (soya beans)	>24 months
High starch content matrices (barley, maize, rye, sorghum and wheat grain)	10 to >31 months
High protein content matrices	not investigated
Other plant matrices (barley, rye, soya bean and wheat straw; soya bean hay)	6 to >24 months
Animal commodities (fat, muscle, liver and kidney from swine, cattle and poultry; milk; eggs)	14 to >26 months

N-acetyl-glyphosate

High acid content matrices	not investigated
High water content matrices (maize forage, green plant and stover; soya bean forage)	6 to >12 months
High oil content matrices (soya beans)	>12 months
High starch content matrices (maize grain)	>12 months
High protein content matrices	not investigated
Other plant matrices (soya bean hay)	>12 months
Animal commodities	not investigated

N-acetyl-AMPA

High acid content matrices	not investigated
High water content matrices (maize forage, green plant and stover; soya bean forage)	>1 to >12 months
High oil content matrices (soya beans)	>1 months
High starch content matrices (maize grain)	>12 months
High protein content matrices	not investigated
Other plant matrices (soya bean hay)	>1 months
Animal commodities	not investigated

2.7.2 Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish

The metabolism of glyphosate in non-tolerant plants was investigated in numerous crops, covering all crop groups. The active substance was applied via soil treatment, hydroponic application, stem or trunk treatment and foliar treatment. Following direct treatment via foliar, trunk, stem or hydroponic treatment unchanged glyphosate was the only significant residue. In presence of soil as a substrate the active substance is quickly degraded, leaving AMPA at

rates comparable or even higher than parent glyphosate. However, the uptake via the roots and the translocation in the plants was very low, not resulting in significant residue levels as confirmed by plant metabolism and confined rotational crop studies. A major part of the glyphosate was degraded into CO_2.

In glyphosate tolerant plants the metabolism may differ significantly. Depending on the kind of modification AMPA (GOX modification), N-acetyl-glyphosate (GAT modification) and N-acetyl-AMPA (GAT modification) become major metabolites in plant commodities, often being present at higher amounts than the unchanged parent. While CP4-EPSPS, an enzyme much lower susceptible to glyphosate, does not affect the metabolic pattern, the ratio between glyphosate and AMPA was approximately 1:1 in GOX modified plants. For GAT modified plants some commodities showed only little glyphosate remaining above the LOQ. N-acetyl-AMPA was the major residue in most commodities while parent glyphosate was only present at low level or even undetected.

The metabolism of glyphosate in rotational crops was investigated in several confined studies involving application rates to bare soil equivalent to 3.87 - 6.5 kg as/ha. The investigation of soil samples in these studies demonstrated the quick degradation of the parent substance, showing AMPA as major residue with levels up to 10 times higher than the glyphosate remaining. TRR levels in samples obtained from rotational crops contained substancial residues, equivalent to concentrations of up to 4.4 mg eq/kg. However, as demonstrated in soil treatment metabolism studies, most of the radioactivity remained unextracted due to incorperation of $^{14}CO_2$ from the degradation of glyphosate in the soil. In the extracts glyphosate levels depended on the interval between treatment and sampling. After short intervals up to 14 weeks glyphosate levels were higher than AMPA (glyphosate: 19.6 - 62 % of the TRR, AMPA: 2.3 - 15.6 % of the TRR). In samples collected after longer intervals glyphosate was only present in minor amounts of 10 % of the TRR or less (absolute levels <0.001 mg eq/kg to 0.026 mg eq/kg) while AMPA was the dominant residue with up to 20 % of the TRR (up to 0.05 mg eq/kg). Further metabolites were not identified.

In livestock animals the metabolism of glyphosate, AMPA and N-acetyl-glyphosate was investigated in lactating goats and laying hens. All three analytes are slowly degraded. Most of the residues was recovered unchanged as administered. The major part of the administered dose was excreted via the faeces. For bioavailable residues the excretion was observed mainly via urine, resulting in highest residue levels found in the kidney. Muscle, fat and milk gave very low residues, normally being present below the LOQ. In liver some metabolisation of glyphosate into AMPA was observed. However, the levels of both analytes were much lower than in kidney. In eggs the residue increase during the whole dosing period of up to eight days. A plateau was observed in livestock feeding studies on laying hens after 14 days. Again, most of the residue was identified as unchanged substance administered.

2.7.3 Definition of the residue

Definition of the residue for plant commodities
Residue definition for enforcement purposes in sweet corn, oilseeds rape, soya beans and maize (non-tolerant and tolerant, all modifications):
sum of glyphosate and N-acetyl-glyphosate, expressed as glyphosate

Residue definition for enforcement purposes in other plant commodities:

glyphosate

Residue definition for dietary intake purposes in plant commodities:
sum of glyphosate, AMPA, N-acetyl-glyphosate and N-acetyl-AMPA, all expressed as glyphosate equivalents

(For the future generation of residue data N-acetly-glyphosate and N-acetyl-AMPA are only mandatory analytes in GAT-modified crops.)

Definition of the residue for animal commodities
Residue definition for enforcement purposes in animal commodities:
sum of glyphosate and N-acetyl-glyphosate, expressed as glyphosate

Residue definition for dietary intake purposes in animal commodities:
sum of glyphosate, AMPA, N-acetyl-glyphosate and N-acetyl-AMPA, all expressed as glyphosate equivalents

(For the calculation of the maximum dietary burden for the purpose of MRL setting, only glyphosate and N-acetyl-glyphosate need to considered, since the reformation of both analytes from AMPA or N-acetly-AMPA is unlikely).

2.7.4 Summary of residue trials in plants and identification of critical GAP

For glyphosate several GAPs were reported:

The application of glyphosate before planting/sowing is reported for all crops involving one to two treatment at 2.16 kg as/ha each. The definition of a PHI was not necessary. A corresponding dataset of supervised field trials covering all crop groups was submitted. In these trials no residues of glyphosate or AMPA above the LOQs of 0.02 mg/kg to 0.05 mg/kg were found except for single detects for cereal straw.

In orchards and vineyards glyphosate is sprayed for weed control onto the ground with up to three applications per year with 2.88 kg as/ha each (maximum of 4.32 kg as/ha and year). Corrresponding supervised field trial data on tree nuts, pome fruit and stone fruit showed no detectable residues above the LOQ of 0.05 mg/kg in the fruits. Special circumstances need to be taken into account for grapes and olives.
For grapes low hanging fruits may be exposed to the spray solution, resulting in residuse up to 0.3 mg/kg in the grapes. For olives ground-picking is a common agricultural practice. Therefore only supervised field trials were taken into account involving ground-picking. The corresponding residues in the olives were between <0.05 mg/kg to 0.93 mg/kg for glyphosate and <0.05 mg/kg to 1.0 mg/kg for the sum of glyphosate and AMPA, expressed as glyphosate.

In oilseeds (rapeseed, linseed and mustard seed) the desiccation two weeks before harvest in conducted with application rates of 2.16 kg as/ha. However no supervised field trial data was submitted matching the reported application rate within the accepted interval of ± 25 %.

Cereal grain (barley, oats, rye and wheat) are also sprayed for desiccation with application rates of 2.16 kg as/ha and a PHI of 7 days. Supervised field trial data matching the GAP are

numerous. For barley and oats grain glyphosate residues were between 1.2 mg/kg and 21.4 mg/kg and for the sum of glyphosate and AMPA, expressed as glyphosate, residues of 1.3 mg/kg to 21.6 mg/kg were found. In wheat and rye grain the parent substance was present at levels between 0.05 mg/kg to 17.5 mg/kg. The total residues (sum of glyphosate and AMPA, expressed as glyphosate) were 0.125 mg/kg up to 18.1 mg/kg.

2.7.5 Summary of feeding studies in poultry, ruminants, pigs and fish

Livestock animal feeding studies were provided for glyphosate, AMPA, glyphosate-trimesium and N-acetly-glyphosate in lactating cows, laying hens and swine.
The residues found in all species were in line with the metabolism studies submitted and covered the calculated mean and maximum dietary burden.

2.7.6 Summary of effects of processing

Under simulated processing conditions glyphosate, AMPA and N-acetyl-AMPA were stable.

The effect of processing was investigated in citrus, potatoes, olives, linseed, rapeseed, soya bean, maize, barley, rye, oats and wheat. In summary glyphosate and AMPA are polar components mainly present on the surface of the commodities analysed. In fatty compartiments (oil) normally no residues above the LOQ were found. An increase in the residue concentration was observed in dried commodities or bran. In view of the high amount of studies please refer to the list of end points or Volume 3 for an detailed overview of processing factors derived.

2.7.7 Summary of residues in rotational crops

In soil glyphosate is quickly degraded into AMPA and finally into CO_2. In experiments conducted as confined rotational crop studies or plants metabolism studies involving soil or hydroponic treatment only a minor uptake via the roots was observed. Both analytes are not further metabolised in the plants, however in rotational crops a higher relative amount of AMPA has to be expected compared to foliar treatment due to its formation in the soil. In confined rotational crop metabolism studies a high degree of incorperation of radioactivity into natural products (carbohydrates, lipids and protein) was observed. The absolute levels of glyphosate rarely exceeded 0.01 mg/kg after treatment at higher application rates (1.07 to 23.2 kg as/ha) than the representative GAPs (up to 4.3 kg as/ha and year). In summary it can be concluded that neither glyphosate nor AMPA show a potential uptake into rotational crops.

Filed studies on the behaviour of glyphosate and AMPA in rotational crops are not required. In supervised field trials involving pre-emergence/pre-sowing application no residues above the LOQ were found except single detect for cereal straw.

2.7.8 Estimation of the potential and actual exposure through diet and other sources

The chronic intake of glyphosate based on the representative uses resulted in a maximum utilisation of 2.5 % of the ADI (0.5 mg/kg bw) for children from Denmark (EFSA PRIMo

Rev. 2). The German NVS II model gave a utilisation of 1.5 % of the ADI for the general population aged 14-80 years.
Due to the low acute toxicological properties of glyphosate and its metabolites the allocation of an ARfD was not necessary.
In summary it can be concluded that the chronic and acute dietary intkae is unlikely to present a public health concern.

2.7.9 Proposed MRLs and compliance with existing MRLs

Based on the representative uses the following MRLs were calculated:

Citrus fruits	0.05* mg/kg
Tree nuts	0.05* mg/kg
Pome fruit	0.05* mg/kg
Stone fruit	0.05* mg/kg
Grapes	0.5 mg/kg
Strawberries	0.05* mg/kg
Root and tuber vegetables	0.05* mg/kg
Bulb vegetables	0.05* mg/kg
Fruiting vegetables, except sweet corn	0.05* mg/kg
Sweet corn	0.1* mg/kg (potential tolerant crop, higher LOQ)
Brassica vegetables	0.05* mg/kg
Leaf vegetables & fresh herbs	0.05* mg/kg
Legume vegetables	0.05* mg/kg
Stem vegetables	0.05* mg/kg
Pulses, except lentils	0.05* mg/kg
Oilseeds, except rape seed and soya beans	0.05* mg/kg
Maize, rape seed, lentils, soya beans	0.1* mg/kg (potential tolerant crop, higher LOQ)
Olives	2 mg/kg
Barley, oats	30 mg/kg
Rye, triticale, wheat	20 mg/kg
Buckwheat, millet, rice, sorghum, others	0.05* mg/kg
Herbal infusions	0.05* mg/kg
Sugar plants	0.05* mg/kg
Swine, muscle, fat and liver	0.05* mg/kg
Swine, kidney	0.2 mg/kg
Bovine, muscle	0.05* mg/kg
Bovine, fat	0.1 mg/kg
Bovine, liver	0.1 mg/kg
Bovine, kidney	2 mg/kg
Milk	0.05* mg/kg
Poultry, muscle, fat and liver	0.05* mg/kg
Poultry, kidney	0.1 mg/kg
Eggs	0.05* mg/kg

In comparision to established MRLs for glyphosate (according to Reg. (EC) 396/2005) the MRLs for barley and oats (20 mg/kg), wheat and rye (10 mg/kg), olives (1 mg/kg) and bovine kidney (2 mg/kg) are lower than the values estimated in this document.

2.7.10 Proposed import tolerances and compliance with existing import tolerances

No import tolerances were reported for glyphosate.

The residues definitions for enforcement purposes in plant and animal commodities are proposed to be amended for compliance with the residue definitions for glyphosate defined by the Codex Alimentarius.

2.8 Fate and behaviour in the environment

2.8.1 Summary of fate and behaviour in soil

2.8.1.1 Aerobic soil degradation

Route and rate of degradation

The degradation route and rate of glyphosate in soil under aerobic conditions was investigated in various soils with different soil characteristics at incubation temperatures of 10 °C, 20 °C and 25 °C and different soil moisture contents. Under aerobic conditions at 10, 20 and 25 °C, glyphosate degrades in soil forming only one soil metabolite AMPA in significant concentrations. The maximum amount of AMPA formed in soil ranged from 13.3 to 50.1 % AR after 8 -91 days. Several other minor components were detected; however, none of these metabolites were formed in amounts greater than 2.3 % AR. At the end of the soil studies (after 60 - 180 days) at 20 °C and 25 °C, 16.9 to 79.6 % AR was mineralized to CO_2 and 2.5 to 43.2 % bound residues were formed. At the end of the study (after 60 days) at 10 °C, 48.2 % AR CO_2 and 2.4 % AR bound residues were formed. Volatiles other than CO_2 remained ≤0.3 % of AR.

Under aerobic conditions, degradation of glyphosate in soil mostly follows mostly biphasic kinetic with a few occasions of SFO kinetic. DT_{50} and DT_{90} values of glyphosate under different soil moisture conditions and temperatures of 20 or 25 °C to be used for persistence calculations range from 1.0 - 67.7 d and from 9.3 - 471.4 d, respectively. At 10 °C, the degradation of glyphosate also followed biphasic kinetic with a DT_{50} value of 8.1 d and a DT_{90} value of 50.8 d. Normalised SFO or back-calculated SFO DT_{50} at 20 °C and pF2 derived from best fit kinetics to be used for evaluation of the P-criterion of potential PBT, vPvB or POP substances range from 3.6 d to 133.8 d with a geometric mean of 18.7 d. The geometric mean of normalised SFO or back-calculated SFO DT_{50} of glyphosate at 20 °C and pF2 to be used for modelling purposes is 21.0 d.

The metabolite AMPA was formed during aerobic degradation of glyphosate at 20 °C and 25 °C with formation fractions between 0.1817 - 0.6076 and mean formation fraction of 0.3680. AMPA subsequently degraded following SFO kinetics with DT_{50} and DT_{90} values under different soil moisture conditions and temperatures of 20 or 25 °C to be used for persistence calculations ranging from 39.0 - 300.7 d and 129.5 - 998.9 d, respectively. The geometric mean of normalised SFO DT_{50} of AMPA at 20 °C and pF2 is 88.8 d.

2.8.1.2 Anaerobic soil degradation

The anaerobic degradation of glyphosate and glyphosate trimesium was investigated for the 2001 EU evaluation of glyphosate and in several newly submitted studies. The results of the new studies demonstrate that glyphosate degrades under anaerobic conditions although at a slower rate than the aerobic conditions when applying more realistic anaerobic conditions found in the arable cropping environment, which are held under an aerobic/anaerobic gradient. Under complete anoxic conditions, as demonstrated in a study submitted for 2001 EU evaluation of glyphosate, glyphosate degradation was negligible.

2.8.1.3 Soil photolysis

In the 2001 EU evaluation of glyphosate several soil photolysis studies were reviewed and considered acceptable by the RMS. In a summary of the study results, it was concluded that the photolytic degradation of glyphosate on soil surfaces to AMPA is a slow process and is, at most, a very minor pathway for the degradation of glyphosate in soil. Therefore, no new soil photolysis studies were submitted by the applicant in the renewal dossier.

2.8.1.4 Field dissipation

The dissipation of glyphosate under field conditions has been investigated at ten sites in Europe (Germany, Switzerland). Glyphosate shows similar degradation rates under field conditions compared with half lives under laboratory conditions. The metabolite AMPA was observed with a maximal occurrence between 19.7 and 53.8 % AR (glyphosate equivalents (molar based)).

A re-calculation of trigger endpoints following FOCUS Kinetics guidance (2006) was provided by the applicant. The un-normalised DT_{50} and DT_{90} values of glyphosate derived from field dissipation studies by best fit-kinetics and used as persistence endpoints and triggers for higher-tier experiments range between 5.7 and 40.9 days and between 66.9 and 386.6 days, respectively. The appropriate DT_{50} and DT_{90} values of the metabolite AMPA range between 283.6 and 633.1 days and between 942.39 and >1000 days, respectively and follow first order kinetics.

For the use in PEC_{Soil} calculation the worst case of the half life values of un-normalised field dissipation studies should be used. In the case of glyphosate in six of eight cases the degradation doesn´t follow first order kinetics, but biphasic models (DFOP and FOMC) were considered best fit kinetics. As input parameters for PEC_{Soil} calculation of glyphosate the kinetic parameters of the DFOP kinetic (k_1, k_2, g) of the trial Kleinzecher, Germany, should be used in the program ESCAPE 2. The overall DT_{50} and DT_{90} values for this trial are 38.3 and 386.6 days for glyphosate.

According to the Draft Guidance on "Evidence needed to identify POP, PBT and vPvB properties for pesticides" of EFSA expert group from 25.09.2012-rev.3 the maximal non-SFO-DT_{90} value divided by 3.32 is relevant with regard to P-criterion. The recalculated SFO-DT_{50} of 116.4 days from trial Kleinzecher, Germany is lower than the trigger of 120 days for PBT substances and therefore, the P-criterion is not fulfilled.

As input parameters for PEC_{Soil} calculation of AMPA the kinetic parameters of the SFO kinetic of the trial Unzhorst, Germany, should be used in the program ESCAPE 2. The DT_{50} value for this trial is 633 days for AMPA.

Normalised field degradation data are not available. Field studies are not triggered by the results from laboratory degradation studies and therefore, not necessary.

2.8.1.5 Adsorption and desorption

The adsorption and desorption behaviour of glyphosate in soil was evaluated during the 2001 EU evaluation of glyphosate. One study (Livingston et al., 1986, BVL no 2325589) was

evaluated as acceptable based on the evaluation criteria and guidance in force at that time. The adsorption/desorption characteristics of glyphosate resulting from this study have been reported in the Glyphosate Monograph and ranged from 3800 to 60000 mL/g (K_{foc} values). The study of Waring (1992, BVL no 1932008) was also evaluated as acceptable. The K_{doc} values reported in the Glyphosate Monograph ranged from 884 to 50660 mL/g.

There are three additional studies of the adsorption and desorption behaviour of glyphosate in soil available from GTF members but not considered during the 2001 evaluation (Thomas and Lane, 1996, BVL no 2310260; van Noorloos and Slangen, 2001, BVL no 2310257; Kolk, 1996, BVL no 2310258), one of which has been evaluated at Member State level already (Thomas and Lane, 1996 BVL no 2310260). Furthermore, there is one more study available (Schneider, 1993, BVL no 1027844) submitted during national authorisation in Germany.

Considering all compliant adsorption/desorption studies of glyphosate in (including already EU evaluated and additional studies), the K_{foc}/K_{doc} values for glyphosate range from 884 to 60000 mL/g (arithmetic mean: 15844 mL/g). The RMS proposes to use 1/n default values of 0.9 in cases where no reliable 1/n value could be derived in the study and 1.0 in cases where no investigations of the relationship between soil solution concentration and adsorption behaviour were conducted in the study.

The adsorption and desorption behaviour of AMPA in soil was evaluated during the 2001 EU evaluation of glyphosate. The adsorption/desorption characteristics of AMPA derived from one acceptable study (Weeden, 1993, BVL no 2325586) have been summarized in the Glyphosate Monograph. K_f and K_{foc} values for AMPA from this study ranged from 15 to 1554 and 1160 to 24800 mL/g, respectively. One additional AMPA adsorption and desorption study (Muller and Lane, 1996, BVL no 2310266), conducted by a GTF member to support its own registrations, has also been evaluated at the EU-Member State level.

Additionally, two studies (Knoch, 2003, BVL no 2310262; Wittig and Bockholt, 2002, BVL no 2310266) with a wide range of soil characteristics were available from GTF members. Neither of these studies was evaluated during the glyphosate 2001 EU evaluation or at EU Member State level.

Considering the results of all compliant adsorption/desorption studies available for AMPA the K_{foc} values for AMPA based on multiple concentration tests range from 1119 to 45900 mL/g (arithmetic mean: 9749 mL/g). The RMS proposes to use 1/n default values of 0.9 in cases where no reliable 1/n value could be derived in the study. The results of all studies show that AMPA has a high adsorption potential.

Table B.2.8-1: Adsorption values for the glyphosate and its metabolite AMPA metabolites

Substance	number of soils (n)	K_{foc}/K_{doc} values (mL/g)		1/n values		Method
		arithmetic mean	range	arithmetic mean	range	
Glyphosate	24	15844	884 - 60000	0.914	0.72 - 1.16	OECD 106
AMPA	16	9749	1119 - 45900	0.853	0.75 - 0.98	OECD 106

2.8.1.6 Predicted environmental concentrations in soil (PEC_{Soil})

The PEC_{Soil} calculations were performed with ESCAPE 2.0 based on the recommendations of the FOCUS workgroup on degradation kinetics (2006). A soil bulk density of 1.5 g/cm^3, a soil depth of 5 cm and a tillage depth of 20 cm (arable crop)/5 cm (permanent crops) were assumed. Initial concentrations, maximum and minimum plateau concentrations, and actual and time weighted average concentrations of glyphosate and AMPA in soil were calculated for a single maximum application rate of 4320 g glyphosate acid/ha as worst case approach and additional for all seven intended uses. It is important to mention that single application rate of 4320 g glyphosate acid/ha is not supported in the representative GAP, but rather represents the recommended maximum total annual application rate for all crops and therefore, a conservative worst-case approach.

For PEC_{Soil} calculations the worst case of the half life values of un-normalised field dissipation studies should be used. As input parameters for PEC_{Soil} calculation of glyphosate the kinetic parameters of the DFOP kinetic (k_1, k_2, g) of the trial Kleinzecher, Germany, should be used in the program ESCAPE 2. The overall DT_{50} and DT_{90} values for this trial are 38.3 and 386.6 days for glyphosate. As input parameters for PEC_{Soil} calculation of AMPA the maximum DT_{50} value of the trial Unzhorst, Germany, of 633 days should be used.

The summary of PEC_{Soil} values for glyphosate and its metabolite AMPA after maximal application of active substance to all crops and for all intended uses are provided in Table B.2.8-2.

Table B.2.8-2: Maximum PEC_{Soil} values for glyphosate and its metabolite AMPA after maximum field applications of 4320 g as/ha to all crops (PEC_{Soil})

Indication	Intended use	Application rate (g/ha) interception (%)	PECact (mg/kg)	PECaccu * (mg/kg)
Glyphosate				
worst case	all crops annual	1 x 4320 (0%)	5.7600	5.974
	all crops permanent	1 x 4320 (0%)	5.7600	6.6162
001	all crops annual	2 x 2160 (0%)	4.7514	4.9572
	all crops permanent	2 x 2160 (0%)	4.7514	5.5746
002	all crop annual	1 x 1080 (0%)	1.4400	1.4935
	all crop permanent	1 x 1080 (0%)	1.4400	1.6538
003, 004	cereals	1 x 2160 (90%)	0.2880	0.2987
005	oil seed rape	1 x 2160 (80%)	0.5760	0.5974
006	orchard crop, vines, citrus&tree nuts	3 x 2880 (0%) only 33% of area treated	2.5490	3.0648
007	orchard crop, vines,	3 x 2880 (0%)	3.8235	4.5973

Indication	Intended use	Application rate (g/ha) interception (%)	PECact (mg/kg)	PECaccu * (mg/kg)
	citrus&tree nuts	only 50% of area treated		
AMPA				
worst case	all crops annual	1 x 4320 (0%)	2.036	3.0719
	all crops permanent	1 x 4320 (0%)	2.036	6.1797

* a tillage depth of 20/5 cm was considered for calculating the background concentration for annual/permanent crops

2.8.2 Summary of fate and behaviour in water and sediment

2.8.2.1 Hydrolysis

Several hydrolysis studies on glyphosate were assessed as acceptable during the EU review of glyphosate (2001) and the results were summarized in the Monograph. Additional studies that were not previously reviewed are available from GTF members (see IIA 2.9.1). In these studies glyphosate was found to be stable to hydrolysis. No significant degradation products have been found in these studies. Therefore, no hydrolysis study for AMPA was conducted. However, because of chemical structure similarity of glyphosate and AMPA and the general observation of the prolonged stability of AMPA in highly alkaline (*e.g.* 0.1 N NH_4OH solvent commonly used to extract glyphosate and AMPA from soil) and acidic aqueous solutions (*e.g.* 6 N HCl elution solvent in AMPA crop method), AMPA also could also be characterized as stable toward hydrolysis.

2.8.2.2 Photolysis

The metabolite aminomethylphosphonic acid (AMPA) does not absorb light significantly at wavelengths longer than 230 nm. Thus, in highly purified sterile water, in which direct photolysis is the only mechanism for photo-transformation, AMPA is expected to be photo-stable. In addition, in accordance with the discussion presented in Annex Point IIA 2.9.2, in regard to the photolysis of [^{14}C]glyphosate in aqueous buffers under the influence of simulated artificial sunlight, it can be concluded that both glyphosate and AMPA should be stable to direct phototransformation in the purified sterile water.

2.8.2.3 Ready biodegradability

In the 2001 EU evaluation of glyphosate, several studies assessing glyphosate's ready biodegradability have been reviewed (Henshal et al., 1972, BVL no 1934355; Brightwell et al., 1978, BVL no 1932009; Wüthrich, 1990, BVL no 1934369; Carrick, 1991, BVL no 2325628; Anonymus, 1990, BVL no 1934372; Neven, 1990a; Neven, 1990b). Two out of these reviewed studies were conducted according to the OECD guideline 302 for test on inherent biodegradability (Wüthrich, 1990, BVL no 1934369; Carrick, 1991, BVL no 2325628). One addition study according to OECD guideline 301 F (Mamometric Respirometry Test) was prepared by a Glyphosate Task Force (GTF) member (Feil, 2009).

In all studies, glyphosate did not show mineralisation of more than 60 % within 28 days. Therefore, the active substance is classified as not ready biodegradable.

2.8.2.4 Water-sediment system

The fate of glyphosate in several different water/sediment systems was evaluated during the 2001 EU evaluation of glyphosate (Möllerfeld and Römbke, 1993, BVL no 1934113; Muttzall, 1993, BVL no 1982136; Steginsky and Powell, 1995, BVL no 1934389; Henshall and Brightwell, 1972, BVL no 1934355; Kesterson and Jackson, 1990; Honegger, 1992, BVL no 2325652; Brightwell, 1978, BVL no 1932052). There is one additional water/sediment study (Bowler and Johnson, 1999, BVL no 2154357) conducted with ^{14}C-glyphosate trimesium. In the initial Annex I submission, an AMPA water/sediment study was not provided by any Notifier; however, one study (Knoch and Spirlet, 1999, BVL no 1934122) was provided later. In addition to the above studies one other glyphosate and three other ^{14}C-AMPA water/sediment studies are available which were not reviewed during the 2001 EU glyphosate evaluation (Heintze, 1996, BVL no 1939626; Feser-Zügner, 2002, BVL no 2310270; McEwen, 2004, BVL no 2310275 and Knoch, 2003, BVL no 2310273).

In summary, the results of the plausible and valid water/sediment studies show that, in addition to microbial degradation, a major contributor to the aquatic dissipation of glyphosate is adsorption to the sediment. They also demonstrated that from approximately 6% to 48% of the applied glyphosate is mineralized to carbon dioxide during 91 or 100 days of incubations. Radioactivity associated with non-extractable residue was between 8% and 35% of the applied glyphosate during 97 or 91 days of incubation. The principal metabolite of glyphosate in water/sediment system is AMPA. The maximum amounts of AMPA detected were 16% (water phase), 19% (sediment) and up to 27 % (total system) of the total glyphosate applied. These studies that were independently conducted with ^{14}C-AMPA as a test substance also established that AMPA quickly dissipates from the water phase by both adsorption to the sediment and by degradation by the sediment micro-flora. Studies demonstrated that from 8% to 40% of the applied AMPA is mineralized to carbon dioxide. Several other minor components were also detected in these studies.

DT_{50} values from all relevant water/sediment studies have been re-calculated according to the recommendations of FOCUS kinetics guidance (FOCUS, 2006, 2011). In most cases, the degradation behaviour of glyphosate in the water/sediment systems does not follow first order kinetics. The recalculated half-life values of glyphosate for the total system ranged between 13.8 and 329.9 days leading to a geometric mean of 67.7 days (n = 6). Water phase DT_{50} values of glyphosate varied between 6.8 and 21.8 days. A geometric mean value of 9.6 days resulted for the water phase. Sediment DT_{50} values of glyphosate ranged between 34.1 and 75.6 days.

The recalculated half-life values of AMPA for the total systems ranged between 69.3 and 102.9 days leading to a geometric mean value of 86.1 days (n = 4). Water phase DT_{50} values of AMPA varied between 2.1 and 15.5 days. A geometric mean value of 5.5 days resulted for the water phase. Sediment DT_{50} values of AMPA could not be derived.

2.8.2.5 Predicted environmental concentrations in surface water, sediment and groundwater (PEC_{SW}, PEC_{Sed} and PEC_{GW}) (IIIA 9.2.1, 9.2.3)

Surface water and Sediment

Predicted environmental concentrations of the active substance glyphosate in surface water (PEC_{SW}) and sediment (PEC_{Sed}) were estimated using the programs FOCUS Steps 1-2 for FOCUS surface water Step 1 and 2 modelling. As worst case covering all intended uses, PEC_{SW} and PEC_{Sed} were derived for pre-emergence application of glyphosate to various field crops and for post-weed emergence use of glyphosate to the soil and trunks of pome/ stone fruit trees representing the intended use in orchard crops, vines including citrus & nut trees (= perennial crops). Additionally, FOCUS surface water Step 1 and Step 2 PEC_{SW} and PEC_{Sed} values were estimated for the metabolites AMPA and HMPA.

For glyphosate, maximum PEC_{SW} and PEC_{Sed} at Step 1 were 104.8 µg/L and 10300 µg/kg, both for the pre-emergence use in field crops and post-weed emergence use in perennial crops. Maximum PEC_{SW} and PEC_{Sed} of glyphosate at Step 2 for the intended pre-emergence use in field crops ranged from 18.49 to 23.58 µg/L and from 1570 to 3600 µg/kg, respectively. For the intended post-weed emergence use in perennial crops, maximum PEC_{SW} of glyphosate at Step 2 were 39.73 µg/L with maximum PEC_{Sed} ranging from 2070 to 4780 µg/kg.

For AMPA, maximum PEC_{SW} and PEC_{Sed} (Step 1) were 40.90 µg/l and 3300 µg/kg, both for the pre-emergence use in field crops and the post-weed emergence use in perennial crops. Maximum PEC_{SW} and PEC_{Sed} at Step 2 for the intended pre-emergence use in field crops ranged from 6.67 to 15.76 µg/l and 628.4 to 1520 µg/kg. For the intended post-weed emergence use in perennial crops, maximum PEC_{SW} and PEC_{Sed} at Step 2 ranged from 7.32 to 17.16 µg/l and 685.1 to 1640 µg/kg.

For HMPA, maximum PEC_{SW} and PEC_{Sed} at Step 1 were 6.71 µg/l and 696 µg/kg, both for the pre-emergence use in field crops and post-weed emergence use in perennial crops. Maximum PEC_{SW} at Step 2 for the intended pre-emergence use in field crops was 1.22 µg/l and maximum PEC_{Sed} ranged from 86.8 to 196 µg/kg. For the intended post-weed emergence use in perennial crops, maximum PEC_{SW} at Step 2 was 2.63 µg/l and maximum PEC_{Sed} ranged from 128 to 294 µg/kg.

Groundwater

Predicted environmental concentrations of the active substance glyphosate and its metabolite AMPA in groundwater (PEC_{GW}) were estimated using the program FOCUS PELMO 4.4.3.

The exposure assessment was based on a representative use pattern derived from the representative GAP, i.e. PEC_{GW} was derived for pre-emergence application of glyphosate to winter cereals and to potatoes, for pre-emergence plus post-harvest application of glyphosate to spring cereals and for post-weed emergence use of glyphosate to pome fruits. A worst-case zero interception was assumed for all applications.

As input parameters for the PEC_{GW} calculations of glyphosate and AMPA the geometric mean of all DT_{50} values (21.03 and 88.84 days, respectively) as well as the arithmetic mean of all K_{oc} values (15844 and 9749 ml/g, respectively) were used.

In all simulations the 80th percentile PEC_{GW} values of glyphosate acid and AMPA at 1 m soil depth were below the groundwater threshold value of 0.1 µg/L indicating that the use of glyphosate as intended is not likely to pose an unacceptable risk to groundwater via direct leaching.

2.8.3 Summary of fate and behaviour in air

Glyphosate has low vapour pressure (1.31×10^{-5} Pa at 25 °C) and therefore significant concentrations are not expected to be found in air through volatilisation following the use of the compound according to the proposed GAP. The 2001 EU glyphosate evaluation concludes that glyphosate can be classified as not volatile based on its Henry's law constant and on volatilization experiments from soil and plants with no significant rates. Due to no significant UV-absorption, direct photolysis in air will not occur. Once in the atmosphere rapid photochemical oxidative degradation of glyphosate will occur.

An atmospheric oxidation rate estimation for the active substance glyphosate based on a calculation procedure by means of quantitative structure reactivity relations (QSAR) developed by Atkinson (AOPWIN (version 1.92) shows a half life of 1.6 hours assuming a OH-radical concentration of 1.5×10^{6} cm^{-3} and a time window of 12 hours. Thus long range transport via air can be excluded.

2.8.4 Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

Surface water
Maximum glyphosate and AMPA concentrations in European surface waters as measured in comprehensive monitoring campaigns (Horth, 2012, BVL no 2310291) range between 1.3 - 370 µg/L and 0.22 - > 200 µg/L for glyphosate and AMPA, respectively. It has to be noted that glyphosate and AMPA monitored in this study exceed the predicted environmental concentrations for glyphosate acid and AMPA in surface water (PEC_{SW}) calculated using the FOCUS (2000) surface water models, even though worst case applications was assumed. Nevertheless, the calculated TER values referring to the monitored concentrations in the study by Horth (2012) with the respective acceptability criteria show that the risk for aquatic organisms is acceptable. Compared to the findings published by Horth (2012), the maximum concentrations which were published in open literature are rather low, namely in the range of 0.4 - 1.37 µg/L and 0.2 - 13 µg/L for glyphosate and AMPA, respectively. Therefore, information published in open literature does not really modify the already existing assessment of glyphosate and AMPA occurrence in surface water.
In addition, control and inspection programs at local authority level in Germany show high rates (35 % in 2009 and 36 % in 2010 during controls that were not event-related) of non-compliance regarding the application of plant protection products on walks and places in housing areas, foot-walks, traffic islands and paved surfaces in private properties (Anonymous, 2011, BVL no 2537364 and Anonymous, 2012, BVL no 2537365). This indicates that misuses of plant protection products on paved surfaces, which often contain glyphosate as active ingredient, by non-professional users occur to a relatively large extent. Therefore, current discussions in Germany are focusing on whether the findings of glyphosate and its metabolite AMPA in surface waters originate to some extent from these misuses of plant protection products containing glyphosate on paved surfaces by non-professional users.

In any event, the other EU Member States should be aware of this problem and, if necessary, take appropriate risk management measures at the national level.

Next to the use of glyphosate based products by non-professional users, we point to the environmental risks associated with the intended uses of glyphosate as desiccant. An herbicide application to time harvest poses additional ecological risks for surface waters and for non-target species (please refer also to chapter 2.9.6). Member States might consider the appropriateness of additional herbicide uses especially when addressing sustainable use of plant protection products according to Directive 2009/128/EC.

Groundwater

Regarding the groundwater monitoring data, it has to be pointed out that glyphosate has been detected in Europe with 0.64% above the limit concentration 0.1 µg/L; and AMPA with 0.77 % above 0.1 µg/L (Horth, 2012, BVL no 2310291). Detailed groundwater monitoring studies demonstrating that glyphosate (at least partly) exceeded 0.1 µg/l are available from Italy (Calliera et al., 2011, BVL no 2310280), Germany (Schmidt and Reichert, 2006, BVL no 2310282), The Netherlands (Franke et al., 2010, BVL no 2310284), Sweden (Carter and Pepper, 2005, BVL no 2310285), France (Anonymous, 2012, BVL no 2310289) and Spain (Sanchís et al., 2012, BVL no 2537361). In some cases, clarification could be presented by the authors; e.g. causes for glyphosate findings in groundwater aquifers > 0.1 µg/L were point source contamination, affection by waste deposit, deficient analysis, no fully protected wells, potential for direct hydrological connectivity between surface water and shallow groundwater via artificial drainage systems and short-term contamination of shallow groundwater or spring water. However, it remains often unclear if findings above the authorisation limit originate from a technically correct and regu-lation compliant use of the respective plant protection products in agricultural areas, or misuses or if construction defects on the groundwater abstraction points are reasonable for the limit exceedances etc. Another emerging issue is that other sources of glyphosate than agricultural applications, e.g. the control of weeds on streams and drains, around railways, roads, sports fields and industrial areas have to be considered as well. Regarding the pathways of glyphosate into groundwater when used for agricultural purposes as intended, RMS considers that groundwater contamination > 0.1 µg/L via direct leaching is generally not expected as the substance is strongly adsorbed to soil particles. Exceptions may be made, e.g. for preferential flow. Within a study from Spain (Sanchís et al., 2012, BVL no 2537361), it is described that surface waters exist in 10 out of 11 sampling sites where glyphosate was (at least partly) detected. Due to this fact, surface run-off and/or drainage into these waters with subsequent bank filtra-tion into groundwater cannot be excluded as pathway. During the EU evaluation of the active substances the pathway surface run-off and drainage into an adjacent ditch with subsequent bank filtration into groundwater is not considered until now.

Within the open literature review, groundwater monitoring data were obtained for 4 EU-countries (Spain, Denmark, Norway and Germany), whereas one citation was found for a non-EU site (Canada). However, information is rather heterogeneous. Maximum glyphosate and AMPA concentrations in either groundwater or drinking water well are in the range of 0.02 - 2.56 µg/L and 0.02 - 0.45 µg/L, respectively, whereas maximum glyphosate and AMPA concentrations as obtained from comprehensive monitoring programs (Horth, 2012, BVL no 2310291) are in the range of 0.01 -24 µg/L and 0.02 - 19 µg/L, respectively. Therefore, information published in open literature does not really modify the already existing assessment of glyphosate occurrence in groundwater.

2.8.5 Definition of the residues relevant to the environment

In the following the residues are defined considering their occurrence in the representative environmental fate studies and for groundwater, in addition, on the basis of PEC_{GW} simulations and the results of lysimeter studies.

Soil
The major residues in soil from the environmental fate point of view are glyphosate and its metabolite aminomethylphosphonic acid (AMPA) (max. occurrence in soil 53.8 % AR).

Ground water
The major residues in soil from representative environmental fate studies are glyphosate and its metabolite aminomethylphosphonic acid (AMPA) (max. occurrence in soil 53.8 % AR).

In all simulations the 80th percentile PEC_{GW} values of glyphosate acid and AMPA at 1 m soil depth are below the groundwater threshold value of 0.1 µg/L indicating that the use of glyphosate as intended is not likely to pose an unacceptable risk to groundwater via direct leaching.

Lysimeter studies usually show that the overall risk for the leaching of glyphosate to groundwater was assessed to be low. Glyphosate was either not detected in the leachate or the mean annual concentrations were significantly below 0.1 µg/l. A similar pattern was observed for its metabolite AMPA. Exceptions may be made, e.g. for soils with low content of organic matter and clays, recharge generated by irrigation and heavy rain, and possible preferential solute transport and/ or colloidal mediated transport.

For these reasons stated above, the definitive relevant residue for further groundwater assessment is defined as glyphosate (parent compound).

Surface water
The major residues in surface water, relevant for further risk assessment from the environmental fate point of view are glyphosate and its metabolites aminomethylphosphonic acid (AMPA) (max. occurrence in the water phase 15.7 % AR and max. occurence in the sediment phase 18.7 %) and hydroxymethylphosphonic acid (HMPA) (max. occurrence in water up to 10.0 % AR).

2.8.6 Summary of exposure calculations and product assessment

Predicted environmental concentrations (PEC's) in soil, surface water, sediment and groundwater were calculated for the active substance glyphosate and its metabolite AMPA. The estimated PEC values for the environmental compartments named above will be used for further risk assessment. From the PEC_{GW} value, it can be concluded that glyphosate and its metabolite AMPA pose no risk to groundwater via direct leaching in Europe.

2.9 Effects on non-target species

2.9.1 Summary of effects on birds and other terrestrial vertebrates

Birds

A number of different avian acute oral, short-term dietary and long-term studies have been carried out with glyphosate acid and are already evaluated during the initial EU assessment of glyphosate acid. New studies not evaluated during the first evaluation of glyphosate in the EU peer review of 2001 have been included ([redacted] 1997, BVL no 2310906; [redacted] 1996, BVL no 2310909; [redacted] 1996, BVL no 2310912; [redacted] 1999, BVL no 2310910; [redacted] 2003, BVL no 2310915).

The following endpoints and effect values have been identified as relevant for the quantitative risk assessment according to the current EFSA Guidance Document:

Concerning the acute risk to birds, it should be considered that large number of acute studies in birds without any mortality at limit doses are available. EFSA guidance document 1438/2009 indicates that "it is permissible to extrapolate an LD_{50} value in cases where there is no mortality or a single mortality at a limit dose in an acute avian toxicity study". Using the study with the bobwhite quail with a limit dose of 2000 mg/kg bw, the extrapolation factor for no mortalities at the limit dose and 20 birds per dose group (the actual number of birds tested at this limit dose exceeded 20), the acute LD_{50} to be used in a bird risk assessment according to EFSA guidance document 1438/2009 is proposed to be 2000 x 2.167 = 4334 mg/kg bw.

Concerning the effects of glyphosate on bird reproduction, studies have been conducted with bobwhite quail ([redacted] 1978, BVL no 2310921 and [redacted], 1999, BVL no 2310916) and mallard duck ([redacted] 1978, BVL no 2310923; [redacted] 1999, BVL no 2310918) for the active substance glyphosate.

The study by [redacted] (1978, BVL no 2310921) is proposed for risk assessment. A significant reduction in egg weight was observed at the highest concentration tested (1000 ppm). Therefore, a NOEC of 18.1 mg a.s./kg b.w./d was determined and agreed during the EU review process. However, changes in egg weight are not considered a standard endpoint in avian reproduction studies anymore according to guideline OECD 206 and has therefore not been adressed in other studies testing higher concentrations. Other relevant endpoints determined in the study of [redacted] (1978) did not show any unacceptable differences compared to the control treatment – including no. of eggs, no. 14 d old survivals and hatchlings weight. The differences in egg weight between control and the treatment with 1000 ppm amounted to a decrease of approx. 7.5 % (10.26 g ± 0.38 g vs. 9.48 g ± 0.47 g in control and 1000 ppm treatment, respectively). Since all parameters concerning hatchling weight and survival were not affected, it can be assumed that the observed changes in egg weight are statistically significant but do not represent a population relevant adverse effect. Therefore, this endpoint will be considered as a NOAEL of 1000 ppm (equivalent to 96.3 mg a.s./kg b.w./d) and is proposed for the assessment of the chronic risk for birds exposed to glyphosate.

Table B.2.9-1: Endpoint values used for the assessment of the risk for birds arising from the exposure to glyphosate

Time scale and type of risk assessment	Test species	Proposed endpoint	Explanation/justification
Acute toxicity	Bobwhite quail *(Colinus virginianus)*	LD_{50} = 4334 mg/kg bw	A large number of acute studies in birds without any mortality at limit doses were submitted. According to EFSA guidance document 1438/2009 the LD_{50} value was extrapolated and is proposed to be LD_{50} = 4334 mg/kg bw
Reproductive toxicity (long-term)	Bobwhite quail (*Colinus virginianus*)	NOAEL = 1000 ppm corr: 96.3 mg/kg bw/d	A NOAEL of 1000 ppm, corresponding to 96.3 mg/kg/bw/d is proposed.

The risk assessment is based on the intended uses of glyphosate acid in the product MON 52276 covering several crops in pre-planting, pre-emergence, pre-harvest and row-application in orchards and vineyards. Regarding the proposed indication pre-planting (post-emergence of weeds), no bare soil scenario is considered as general scenario since the mode of action of glyphosate is via uptake by green tissues of leaves and stems of treated plants. Therefore, a leaf development is assumed in the assessment scenario.
The maximum cumulative application rate per year is set to 4.32 kg glyphosate/ha. The maximum application rate per treatment is 2.16 kg glyphosate/ha, except for spot applications in orchards and vines where the maximum application rate is 2.88 kg glyphosate/ha.

Based on the screening assessment step, the calculated TER values resulting from an exposure of birds to glyphosate reach the acceptability criteria TER ≥ 10, according to Regulation (EU) No 546/2011, Annex, Part I C, 2. Specific principles, point 2.5.2. for acute effects. The results of the assessment indicate an acceptable risk for birds due to uptake of contaminated food after use of MON 52276 in the indications according to the label.

Based on Tier 1 assessment step, the calculated TER values for the long-term risk resulting from an exposure of birds to glyphosate according to the intended use in oilseed rape (late (with seeds); rapeseed, mustard seed, linseed; BBCH 88-99) and cereals (cereals, late season) as well as in orchards (vines including citrus & and tree nuts, post emergence of weeds; 28 days interval between applications with spot treatment round of trunks or application to the intra-rows) achieve the acceptability criteria TER ≥ 5 according to Regulation (EU) No 546/2011, Annex, Part I C, 2. Specific principles, point 2.5.2. for long-term effects. The results of the assessment indicate an acceptable risk for birds due to the intended use according to the label.

For the intended use in the scenario "all crops (all seeded or transplanted crops)" with an application rate of max. 2 x 2160 g a.s./ha the decline of glyphosate residue in grass was used in the risk assessment for birds feeding on grass foliage. Based on refined assessment step, the calculated TER values for the long-term risk resulting from an exposure of birds to glyphosate achieved the acceptability criteria TER ≥ 5.

In addition to their diet, birds may also be exposed to glyphosate via drinking water. For glyphosate, the ratio of highest application rate (4320 g a.s./ha) to lowest relevant endpoint (NOAEL = 96.3 mg a.s./kg bw/d) indicated an acceptable risk from exposure to contaminated drinking water without the need for further calculations.

The metabolite AMPA has been tested in several toxicity studies which demonstrated that it is of lower toxicity than glyphosate acid (see Volume 1, chapter 2.6.8). Moreover, most of the parent glyphosate is eliminated unchanged and only a small amount (less than 1% of the applied dose) is transformed to aminomethylphosphonic acid (AMPA). Therefore it can be concluded that the risk to birds will be acceptably low and no further quantitative risk assessment is conducted. Since the log K_{ow} values of glyphosate is logP < -3.2 (pH 2-5, 20 °C), the active substance is deemed to have a negligible potential to bioaccumulate in animal tissues.

Overall, the risk to birds from the intended uses of glyphosate is considered to be acceptable.

Terrestrial vertebrates
For the first EU peer reviewed evaluation of glyphosate in 2001, a large number of toxicity studies were submitted that had been conducted with either glyphosate acid or its salts. For the current re-evaluation of glyphosate, several additional studies in rats, mice and rabbits with administration of glyphosate acid were provided (see Vol.3, B.6.2.1). For further details please refer to Volume 3, B.6.2.1.

The acute mammalian toxicity of glyphosate is low in the species tested. The oral LD_{50} was above 2000 mg/kg bw. General signs of oral intoxication were breathing difficulties, reduced activity, ataxia, piloerection, convulsions and hunched posture. For further details please refer to Volume 3, B.6.2.1. For risk assessment an $LD_{50} \geq 2000$ mg/kg bw is proposed. For further details please refer to Volume 3, B.6.2.1.

The developmental toxicity and teratogenicity of glyphosate were tested in several studies in rats and rabbits. In general rabbit proved to be more sensitive than rats. The lowest NOAEL for developmental effects was 50 mg/kg bw/day, based on post-implantation losses at 200 mg/kg bw/day in the test species rabbit. In other studies the NOEAL were consistently below 200 mg/kg bw/day due to post-implanation losses and late embryonic death (please refer to RAR, Vol 1, chapter 2.6.7.2.2.). As population relevance can not be excluded due to the clinical parameters observed, an overall NOAEL of 50 mg/kg bw/day is proposed for risk assessment.

Based on the presumptions of Tier 1, the calculated TER values for the risk resulting from an exposure of mammals to the active substance glyphosate according to the GAP of the formulation MON 52276 reach the acceptability criteria TER ≥ 10, according to Regulation (EU) No 546/2011, Annex, Part I C, 2. Specific principles, point 2.5.2. The results of the assessment indicate an acceptable risk for mammals.

For the serial application of 2 ×max. 720 g a.s./ha and once max. 2880 ga.s./ha the results of the worse case assessment indicate a low risk for small herbivorous mammals due to uptake of contaminated food.

Based on Tier 1 assessment step, the calculated TER values for the long-term risk resulting from an exposure of mammals to glyphosate do not achieve the acceptability criteria TER ≥ 5. The results of the assessment indicate an unacceptable risk for small herbivorous mammals due to the intended uses according to the label. A refined risk assessment was considered necessary.
The refinement for the long-term risk is achieved via the consideration of the glyphosate decay in plant material over time. Based on refined assessment step, the calculated TER

values for the long-term risk resulting from an exposure of mammals to glyphosate achieved the acceptability criteria TER ≥ 5 for the intended uses in "all crops", "crop maturity in cereals", "crop maturity in oilseed rape".
For the post emergence treatment of weeds orchard crops (vines including citrus & tree nuts, intrarow & spot treatment) the calculated TER values for the long-term risk resulting from an exposure of mammals to glyphosate do not achieve the acceptability criteria TER ≥ 5. Nevertheless, risk can be mitigated as the results of the assessment with a serial application of 3 × max.1440 g a.s./ha indicate a acceptable risk for small herbivorous mammals due to uptake of contaminated food.

In addition to their diet, mammals may also be exposed to glyphosate via drinking water. For glyphosate, the ratio of highest application rate (4320 g a.s./ha) to lowest relevant endpoint (NOAEL = 50 mg a.s./kg bw/d) indicated an acceptable risk from exposure to contaminated drinking water without the need for further calculations.

The metabolite AMPA has been tested in several toxicity studies which demonstrated that it is of lower toxicity than glyphosate acid (see Vol 1, chapter 2.6.8). Moreover, most of the parent glyphosate is eliminated unchanged and only a small amount (less than 1 % of the applied dose) is transformed to aminomethylphosphonic acid (AMPA). Therfore it can be concluded that the risk to mammals will be acceptably low and no further quantitative risk assessment is conducted. Since the log K_{ow} values of glyphosate is logP < -3.2 (pH 2-5, 20 °C), the active substance is deemed to have a negligible potential to bioaccumulate in animal tissues.

RMS considers the provision of a scientifically sound ecological risk assessment to be coupled to the assessment of the impact of herbicide use on the diversity of terrestrial non-target species due to indirect effects via food web interference. The effects trace back to the intended effect of the herbicides – eliminating competing plants – which is virtually the same in all broad spectrum herbicides. Even though these effects are not substance-specific but rather caused by the use of herbicides per se, the RMS considers it necessary to address this issue in the context of the evaluation of the active substance glyphosate since it represents the far the most extensively used herbicides. Glyphosate can actually be regarded as the most significant herbicide with indirect effects on terrestrial vertebrates (and invertebrates) of the agricultural landscape. The scientific evidence regarding negative impacts of the use of herbicides on terrestrial vertebrates is mostly confined to the farmland birds (see DEFRA, 2005; [redacted] 2013); whereas information with respect to farmland mammals is very limited. Previous studies on potentially affected farmland bird species such as Grey Partridge demonstrate the population relevance of indirect effects of herbicides. For instance in the study of [redacted]. (2001), a relationship between pesticides, food availability, breeding performance and population size has been fully demonstrated with herbicides being the main determining pesticide group. Chick survival is the key factor determining population development and Grey Partridge chicks are highly dependent on invertebrate prey abundance in arable crops, mainly cereals, where they feed on insects and other arthropods along the edges ([redacted] 1971; [redacted] 1985). The impact of the herbicide use via food chain interactions seems to be the most relevant indirect effect of PPPs although the interference with habitat quality (e. g. cover) and resulting changes in the predation risk might also play a significant role for some species or groups. For those species that depend on arable land as habitat, thus potentially affected by the PPP use due to interference with the food availability or habitat quality, the consideration of indirect effects in the risk regulation of PPPs can be regarded necessary from both the scientific as well as from the legal perspective. In previous evaluations of active substances, this kind of effect has not been assessed, and standardized

assessment methods are not yet available. However, according to the new data requirements (Regulation (EU) No 283/2013) the potential impact of the active substance on biodiversity and the ecosystem, including potential indirect effects via alteration of the food web, shall be considered. In the opinion of the RMS it is not a feasible and sustainable option to ignore indirect effects. Effective and reasonable risk mitigation measures are available (compensation measures, especially cropped no-spray zones, fallow land and flowering margins) but yet have to be established in the regulation of PPP. As the severity of indirect effects of herbicide use on farmland bird (and mammal) species diversity strongly depends on agricultural and landscape properties, an assessment considering all different conditions all over the EU is hardly possible. Thus, we limit to describe the high potential of glyphosate and other broad spectrum herbicides to cause indirect effects and to highlight the need for risk mitigation measures by the member states, proposing compensation measures as a suitable tool.

2.9.2 Summary of effects on aquatic organisms

The toxicity of glyphosate as the acid, the isopropylamine (IPA) salt, the potassium (K) salt and its metabolites AMPA and HMPA to aquatic organisms as well as the representative formulation in the present approval renewal of glyphosate (MON 52276) was investigated in a series of laboratory studies with representative species from different trophic levels of the aquatic food chain (i.e. fish, aquatic invertebrates, algae and aquatic plants). A summary of the relevant acute and long-term endpoints, representing the worst case for key species are presented in the table below:

Table B.2.9-2: Endpoints for aquatic species (most sensitive species of each group) relevant for the quantitative risk assessment

Species	Substance/ Test item	Test design	Toxicity	Endpoint	Safety factor
			(mg test item/L)		
O. mykiss	Glyphosate acid	acute	38	mortality	100
L. macrochirus	Glyphosate IPA-salt	acute	>1000 741 a.s.	mortality	100
O. mykiss	Glyphosate K-salt	acute	>2573 1227 a.s	mortality	100
O. mykiss	AMPA	acute	520	mortality	100
O. mykiss	MON 52276	acute	> 989 > 306 a.s.	mortality	100
B. rerio	Glyphosate acid	long-term	5.6 (recalc. by RMS)	mortality	10
P. promelas	AMPA	long-term	12	hatching success, fry survival, length and weight	10
Daphnia magna	Glyphosate acid	acute	40	immobilization	100
Daphnia magna	Glyphosate IPA salt	acute	930	immobilization	100
Daphnia magna	Glyphosate K-salt	acute	592 278 a.s. (recalc. by RMS)	immobilization	100
Daphnia magna	AMPA	acute	690	immobilization	100
Daphnia magna	HMPA	acute	>100	immobilization	100
Daphnia magna	MON 52276	acute	676 209 a.s.	immobilization	100
Daphnia magna	Glyphosate acid	long-term	12.5	reproduction	10

Species	Substance/ Test item	Test design	Toxicity	Endpoint	Safety factor
			(mg test item/L)		
			(recalc. by RMS)		
Daphnia magna	AMPA	long-term	15	reproduction	10
S. costatum	Glyphosate acid	chronic	11	biomass	10
			18	growth rate	10
A.flos-aquae	Glyphosate acid	chronic	8.5	biomass	10
			22	growth rate	10
P.subcapitata	Glyphosate IPA salt	chronic	9.25	biomass	10
			31	growth rate	10
D.subspicatus	AMPA	chronic	89.8	biomass	10
			452	growth rate	10
P.subcapitata	HMPA	chronic	> 115	biomass	10
			> 115	growth rate	10
P.subcapitata	MON 52276	chronic	178	biomass	10
			393	growth rate	10
Lemna gibba	Glyphosate acid	chronic	12	frond count	10
Lemna minor	Glyphosate-IPA salt	chronic	25.5	frond count	10
Lemna gibba	HMPA	chronic	> 123	frond count	10
Lemna gibba	MON 52276	chronic	21	frond count	10
M.aquaticum	MON 77973 Glyphosate acid	chronic	12.3	fresh weight, relative increase	10
M.aquaticum	MON 52276	chronic	4.4	fresh weight, relative increase	10
M.aquaticum	AMPA	chronic	31.1	root length, relative increase	10

The principal metabolite of glyphosate in water/sediment system is AMPA. The maximum amounts of AMPA detected were 16 % (water phase), 19 % (sediment) and up to 27 % (total system) of the total glyphosate applied. This indicates that there is a potential for exposure to glyphosate for sediment-dwelling organisms. However, the NOEC values from the long-term *Daphnia* test with glyphosate acid are well above 0.1 mg/L, indicating low toxicity to aquatic invertebrates. According to the GD on Aquatic Ecotoxicology SANCO/3268/2001 rev.4, specific toxicity studies on sediment-dwellers should therefore not be necessary.

As worst case covering all intended uses, PEC_{SW} and PEC_{Sed} were derived for pre-emergence application of glyphosate to various field crops and for post-weed emergence use of glyphosate to the soil and trunks of pome/stone fruit trees representing the intended use in orchard crops, vines including citrus & nut trees (= perennial crops).

Calculated TER values referring to FOCUS Step 1 and 2 are provided in the following table:

Scenario	App. rate (g/ha)	PEC_{sw} (µg/L)	Fish		Invertebrates		Algae	Aquatic plants
			acute	prolonged	acute	prolonged		
			O. mykiss	*B. rerio*	*D. magna*		*A. flos-aquae*	*M. aquaticum* (MON52276)
			LC_{50} (µg/L)	NOEC (µg/L)	EC_{50} (µg/L)	NOEC (µg/L)	E_bC_{50} (µg/L)	E_bC_{50} (µg/L)
			38000	5600	40000	12500	8500	4400
			TER					
FOCUS Step 1 Not crop specific	1×4320	104.81	363	53	382	119	81	42

FOCUS Step 2 North EU (Oct-Feb)	2×2160	23.58	1612	237	1696	530	360	188
North EU (Mar - May) (Jun-Sep)	2×2160	18.49	2055	303	2163	676	460	240
South EU	2×2160	19.30	1969	290	2073	648	440	230
TER criterion			100	10	100	10	10	10

Comparison of calculated TER values with the respective acceptability criteria clearly shows that the risk for aquatic organisms is acceptable.

2.9.3 Summary of effects on arthropods

2.9.3.1 Effect on bees

The 2001 EU glyphosate evaluation concluded that the hazard quotient values for intended uses of glyphosate are well below 50, indicating a low risk to honeybees according to the EPPO risk assessment scheme. In order to reevaluate glyphosate a total of seven laboratory toxicity studies with technical or formulated glyphosate, a tunnel test and a study about the honeybee brood development with technical glyphosate were submitted. The results from new laboratory toxicity studies demonstrate that glyphosate, glyphosate salts and MON 52276 have very low acute contact and oral toxicity to honeybees with LD50 values around or higher than 100 µg a.s./bee. The calculated HQ values show an acceptable risk for honeybees due to the intended use of the lead formulation MON 52276 according to the label.

Additionally a bee brood study was performed following established methodology which demonstrates that glyphosate poses no chronic risk to bee brood as well at worst case field exposure levels.

2.9.3.2 Effects on other arthropod species

Several studies on the effect of glyphosate formulations on non-target arthropods were assessed during the first EU evaluation of glyphosate in 2001 and are summarised in SANCO/6511/VI/99-final. These studies were evaluated in the monograph but were not submitted with the renewal dossier and are not documented in detail in this Review Assessment Report. Additional studies with the lead formulation MON 52276 have been conducted with *Aphidius rhopalosiphi*, *Typhlodromus pyri* and *Aleochara bilineata* to meet the data requirements that are acceptable for an updated non-target arthropod risk assessment. The following endpoints and effect values have been identified as in principle relevant for the quantitative risk assessment:

Table B.2.9-3: Toxicity of MON 52276 to non-target arthropods submitted for the present application for renewal of approval for glyphosate

Species	Substance	System	Results

Aphidius rhopalosiphi	MON 52276	Extended laboratory (whole plant), 3D	LR_{50} > 16.0 L product/ha (5760 g a.s./ha)
Typhlodromus pyri	MON 52276	Extended laboratory (leaf discs), 2D	$ER_{50} \geq$ 12.0 L product /ha (4320 g a.s./ha)
Aleochara bilineata	MON 52276	Extended Laboratory (soil)	ER_{50} > 12.0 L product /ha (4320 g a.s./ha)

With regard to the endpoints from the extended laboratory tests regarding lethal and sublethal effects and the predicted rates of glyphosate in-field as well as off-field, all calculated HQ values remain below the acceptability criterion. The calculated HQ values show an acceptable risk for non-target arthropods due to the intended use of the lead formulation MON 52276 according to the label.
Apart from potential direct (i.e. toxicological) effects, non-target arthropods can be affected indirectly by the use of herbicides. These effects trace back to the intended effect of the herbicides – eliminating competing plants – and the interruption of the food web going along with it. Considering the strong evidence that the use of herbicides (including glyphosate) considerably contributes to the ongoing loss of biodiversity in farmland invertebrate and vertebrate non-target species additional risk mitigation measures might be regarded at member state level depending on the agricultural and landscape conditions.

2.9.4 Summary of effects on non-target soil meso- and macrofauna

Earthworms

For evaluation of acute risk of glyphosate acid on *Eisenia fetida*, we propose to use the endpoint LC_{50} > 5600 mg a.s./kg dry soil from the newly submitted test. For the evaluation of the long-term risk, a new chronic study was submitted. In this study no statistically significant effects were observed. Therefore the proposed endpoint is a NOEC = 1000 mg MON0139/kg dry soil, corresponding to 473 mg of glyphosate acid.
AMPA was classified as a major metabolite occurring in relevant amounts (1 x ≥ 10% of application rate in soil. For AMPA, in a new acute toxicity study the LC_{50} of AMPA was determined to be > 1000 mg AMPA/kg dry substrate. A new study concerning the long-term toxicity of AMPA towards earthworms was performed. For this study a re-evaluation of the deriven endpoints was performed by the RMS. A NOEC of 131.9 mg/kg was recalculated for biomass deviation and number of juveniles, due to a significant reduction in offspring number observed in treatment concentrations higher than 131.9 mg AMPA/kg dry soil. The 56-day no-observed-effect-concentration of AMPA was 131.9 mg/kg regarding earthworm reproduction (number of juvenils).

MON 52276 is the leading formulation in the Annex I re-registration dossier of glyphosate. A study with MON 52276 was conducted leading to an LC_{50}>1250 mg/kg soil dry soil (IPA-salt) corresponding to >388 mg a.s/kg dry soil.

According to the GAP, glyphosate containing plant protection products are intended to be applied at maximum application rate of 2 x 2160 g a.s./ha. The maximum application rate is supposed to be 4.32 kg/ha glyphosate in any 12 month period across use categories.
TER values were calculated for glyphosate and the metabolite AMPA for a worst-case scenario with an application rate of 4.32 kg/ha glyphosate. The results of the assessment

indicate an acceptable acute and long-term risk for earthworms due to the intended use according to the label.

Soil mesofauna

New studies have been conducted exposing *Hypoaspis aculeifer* and *Folsomia candida* to glyphosate IPA salt and AMPA, respectively. The following endpoints and effect values have been identified as in principle relevant for the quantitative risk assessment:

Table B.2.9-4: Toxicity of glyphosate IPA-salt and its metabolite AMPA to soil mites and springtails

Species	Substance	Design	Endpoints (mg/kg dry soil)
Hypoaspis aculeifer	Glyphosate IPA-salt	14 d chronic	EC_{50} > 1000; > 472.8 a.e NOEC=1000; 472.8 a.e.
Folsomia candida	Glyphosate IPA-salt	28 d chronic	EC_{50} >1000; > 587 a.e. NOEC= 1000; 587 a.e.
Hypoaspis aculeifer	AMPA	14 d chronic	EC_{50} > 320 NOEC=320 mg/kg dry soil
Folsomia candida	AMPA	28 d chronic	EC_{50} >315 NOEC= 315

The TER values calculated using worst-case PEC_{SOIL} values for glyphosate acid and its metabolite AMPA - the maximum application rate is supposed to be 4.32 kg/ha glyphosate in any 12 month period across use categories - exceeded the relevant triggers, indicating that the risk to soil macro- and mesofauna acceptable.

2.9.5 Summary of effects on soil nitrogen transformation

MON 52276 is the representative formulation in the current EU review of glyphosate. MON 52276 as well as the metabolite AMPA caused no significant effects > 25 % on soil microflora respiration and soil nitrogen transformation processes. Based on laboratory testing with MON 52276, the Annex VI trigger value of > 25 % effects after 28 days was not exceeded at concentrations of 1× and 5× the maximum recommended annual use rate for 4.32 kg a.s./ha. Therefore, the use of MON 52276 according to the proposed use pattern can be considered not to result in any unacceptable adverse effects for soil micro-organisms.
For the active ingredient glyphosate effects on the nitrogen cycle test could not be assessed due to an invalid study according to OECD guideline 216. According to the OECD 216 guideline the test concentrations recommended are the maximum predicted environmental concentration (PEC) and five times that concentration. Sufficient data was submitted to evaluated the risk of the representative formulation MON 52276.

Nevertheless, for the evaluation of the active substance glyphosate acid, further data will have to be generated to assess the risk for non target micro-organisms. This is necessary as the active substance glyphosate acid is considered persistent in soil (the maximum DT_{50} value of unnormalised field dissipation studies of 116.4 days exceeds the trigger value of 60 days for soil).

2.9.6 Summary of effects on terrestrial non-target higher plants

In the first EU peer review evaluation of glyphosate in 2001, no risk assessment for terrestrial plant was performed, but studies on seed germination and seedling emergence and one study on vegetative vigour were evaluated. New studies on seedling emergence and vegetative vigour of terrestrial non-target plants have been carried out with glyphosate acid and the lead formulation MON 52276.
The potential effects of glyphosate acid on seedling emergence could not suffuciently demonstrated as the study submitted is not considered as valid by the RMS.
So far, for risk assessment in the national and EU plant protection product authorization process, the lowest ER_{50} values in a vegetative vigour test after 21 days was observed for tomato plants and the endpoint was calculated to be 0.146 kg a.s./ha for dry weight. The new vegetative vigour study of glyphosate acid on non-target terrestrial plants did not include the most sensitive species tomato. The lowest ER_{50} values in the new study was calculated after 28 days for oilseed rape to be 0.149 kg glyphosate acid/ha and 0.150 kg glyphosate acid/ha, respectively for visual damage assessment and plant dry weight. The risk might not be reliably predicted and the assessement based on the endpoint for the active ingredient glyphosate acid can be considerd on a preliminary basis. The former EU endpoint $ER_{50,\ 21\ day}$ for tomato plants = 0.146 kg a.s./ha for dry weight is proposed for risk assessment.

For the evaluation of the representative plant protection product MON 52276, further data will have to be generated. It can not be excluded that the formulants in the product enhance toxicity. A valid study assessing effects on non-target plants is required for the plant protection product. The test shall provide the ER_{50} values of the plant protection product to non-target plants.

It is evident from the available PPP authorization data, that the glyphosate-containing formulated products are typically about a factor of 3 more toxic than the active ingredient itself (confidential data not shown). In order to follow a precautionary principle, in a preliminary risk assessment for non-target plants, the acceptability criterion is modified as follows when assessing glyphosate-based formulated products: TER ≥ 15 instead of TER ≥5.

Based on the predicted rates of glyphosate in off-field areas, the TER values describing the risk for non-target plants following exposure to glyphosate indicate acceptable risks providing that the following risk mitigation measures are taken into account:

Table B.2.9-5: Proposed risk mitigation measures for the achievemnt of an acceptable risk for non-target plants in off-field areas

Intended uses	Application rate (g a.s./ha)	Buffer strip (m) without drift reduction	Buffer strip (m) with 90% drift reduction
Orchard crops, vine including citrus & tree nuts*	1 x 2880	5 m	-
	1 x 2160	5 m	-
	3 x 1440	5 m	
All crops (all seeded and transplanted crops)	2 × 2160	10 m	-
	2 × 1440	10 m	-
	1 × 1440	5 m	-
	1 × 1080	5 m	-
Cereals, Oilseeds (pre-harvest) *	1 x 2160	trigger not reached	5m
	1 × 1440	10 m	-
	1 × 1080	10 m	-
	1x 720 g	5 m	-

* In the case of the intended use on mature crops before harvest, the drift rate to be considered should mirrow the height of the plants. The exposure scenario "ground crops x 2" was chosen.

Acceptability criteria are not met for the intended use 'pre-harvest' in cereals and oilseeds with one application rate at 1 x 2160 g a.s./ha,. The risk for non-target plants arising from this intended use are considered unacceptable without drift reduction. If 90 % drift reduction nozzles are used, acceptable risk is achieved in several scenarios at 1 m. For the cereals scenario with an application rate of max. 1 x 2160 g a.s/ha we propose both the use of 90 % drift reduction nozzles and a buffer of 5 m.

A late herbicide application before harvest time poses additional ecological risks for surface water, ground water and for non-target species. We refer to Directive 2009/128/EC of the European Parliament and of the Council that establishes a framework for Community actions to achieve a more sustainable use of pesticides (Plant Protection Framework Directive). Directive 2009/128/EC commit Member States to adopt national action plans (NAP) for sustainable use of plant protection products in Article 4. The aims are to further reduce the risks and impacts to human health and the natural environment associated with the use of pesticides and to limit the application of pesticides to the necessary degree. Member States might consider the appropriateness of additional herbicide uses, especially when addressing sustainable use of plant protection products according to Directive 2009/128/EC.

The protection aims according to Regulation EC 1107/2009 – the absence of unacceptable effects on biodiverstity and the ecosystem – do not explicitly differentiate between in- and off-field habitats. Considering the flora species as an integral part of the biodiversity of non-target species and the strong evidence that the use of herbicides including glyphosate contributes to the ongoing loss of biodiversity in farmland invertebrate and vertebrate (especially farmland bird) species additional risk mitigation measures might be regarded at member state level depending on the agricultural and landscape conditions.

2.9.7 Summary of effects on biological methods for sewage treatment

Measurements of the oxygen consumption of glyphosate acid in activated sludge resulted in EC_{50}-values of > 100 mg/L. Glyphosate acid did not exhibit any significant symptoms up to the highest test concentrations. Because glyphosate acid has shown a low bactericidal activity a risk to biological sewage treatment is not expected.

2.9.8 Summary of product exposure and risk assessment

The risk assessment for birds and mammals is based on the active ingredient glyphosate acid in the product MON 52276 for the intended uses in several crops including pre-planting, pre-emergence, pre-harvest and row-application in orchards and vineyards.

The results of the assessment indicate an acceptable acute risk for birds due to uptake of contaminated food after use of MON 52276 in the indications according to the label. Based on refined assessment step for the long-term risk (decline of glyphosate on grass), the calculated TER values for the long-term risk resulting from an exposure of birds to glyphosate also achieved the acceptability criteria TER ≥ 5.

The calculated TER values for the acute risk assessment resulting from an exposure of mammals to the active substance glyphosate in the formulation MON 52276 indicate an acceptable acute risk due to uptake of contaminated food after use of MON 52276.

For the serial application of 2 × max. 720 g a.s./ha and 1 × max. 2880 ga.s./ha the results indicate a low risk for small herbivorous mammals due to uptake of contaminated food. However, in orchards, as glyphosate is not applied to the grassy alleys between the tree lines (or the foliage of the trees) there might be other non contaminated vegetation for herbivores to graze. Moreover the LD_{50} > 2000 mg/kg/day represents a worse case assumption for the use in acute oral wildlife risk assessment.

The calculated TER values for the long-term risk resulting from an exposure of small herbivorous mammals to glyphosate do not achieve the acceptability criteria TER ≥ 5 with the maximum application rates for the post emergence treatment of weeds in orchard crops. Risk can be mitigated with a serial application of 3 × max.1440 g a.s./ha indicating an acceptable risk for small herbivorous mammals.

Comparison of calculated TER values with the respective acceptability criteria shows that the risk for aquatic organisms is acceptable.

The calculated HQ values show an acceptbale risk for non-target arthropods due to the intended use of the lead formulation MON 52276 according to the label.

A valid study on N-mineralisation should be submitted.

For the evaluation of the lead formulation MON 52276 on non-target plants, data will have to be generated. A valid study on the effects of MON 52276 on vegetative vigour is required. The lack of a valid study with the plant protection product MON 52276 to non target plants is taken into account by a higher safety factor in the risk assessment (15 instead of 5).

Depending on the agricultural and ecological conditions, the use of gyphosate and other broad spectrum herbicides may affect the populations of non-target terrestrial arthropod and vertebrate (especially farmland bird) species via trophic interactions. These effects trace back to the intended effect of the herbicides – eliminating competing plants – and the interruption of the food web going along with it.

2.10 Classification and labelling

2.10.1 Proposals for the classification and labelling of the active substance

The only proposed classification and labelling of the active substance glyphosate (acid) is for eye irritating properties. A respective justification is given in section 2.6.2.

According to Directives 67/548/EEC, glyphosate acid is to be labelled and classified with **Xi ('Irritant')** and **R41 ('Risk of serious damage to eyes'),** *i.e.*, the current classification should be maintained.

Corresponding to the GHS criteria, the appropriate classification and labelling **is 'Irreversible effects on the eye / serious damage to eyes (Category 1)', H318**.

Substance	Species	Test design	Toxicity (mg /L)
Glyphosate acid	*Oncorhynchus mykiss*	acute	38.0
	Brachydanio rerio	Long-term	5.6
	Daphnia magna	acute	40.0
		Long-term	12.5
	Skeletonema costatum	acute	18
		Long-term	1.82
	Lemna gibba	acute	12.0
		Long-term	3.0
Biodegradability:	Classified as not readily biodegradable (see 2.8.2.3)		

Based on Commission Regulation 790/2009 (amending EC regulation 1272/2008 (CLP))

Hazard Symbol(s):	none	
Classification:	none	
Signal word(s):	none	
Hazard statement:	none	
Precautionary statement:	none	

2.10.2 Proposals for the classification and labelling of preparations (Annex IIIA 11.3 and 11.4)

For the preparation MON 52276 the following classification/labelling is proposed in accordance with Directives 67/548/EEC and 1999/45/EC:

None

According to the criteria given in Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008, the following classification/labelling for toxicological hazards of the preparation is proposed:

None

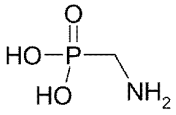
'15.8 percent of the mixture consist of ingredients of unknown inhalation toxicity.'

2.11 Relevance of metabolites in groundwater

2.11.1 STEP 1: Exclusion of degradation products of no concern

The following metabolite was identified in soil degradation studies as potentially relevant for groundwater, due to the exceedance of the pertinent trigger values on formation in soil.

Table 2.11-1: Metabolites detected in soil degradation studies which fulfil the criteria according to SANCO/221/2000- rev.10-final (2003)

Metabolite	Stucture/ molecular formula	Molecular weight (g/mol)	maximal occurrence in soil (%) after n days (reference)
AMPA Aminomethylphosphonsäure	 CH_6NO_3P	111.04	53.8 % after 271 days (Schulz 1992, BVL no 1932133 / trial Menslage)

This chemical structure does not fulfil the criteria for being excluded as a degradation product of no concern (inorganic compound not containing a heavy metal; short aliphatic chain without alerting chemical moieties; non-toxic natural product). Hence, this metabolite has to be considered further in Step 2 of the tiered relevance assessment.

2.11.2 STEP 2: Quantification of potential groundwater contamination

Based on $FOCUS_{GW}$ calculations with the relevant input parameters, a potential to exceed groundwater concentrations of 0.1 µg/L was not identified for the metabolite AMPA, therefore it has not to be considered further in Step 3 of the tiered relevance assessment.

2.11.3 STEP 3: Hazard assessment – identification of relevant metabolites

2.11.3.1 STEP 3, Stage 1: screening for biological activity

-/-

2.11.3.2 STEP 3, Stage 2: screening for genotoxicity

-/-

2.11.3.3 STEP 3, Stage 3: screening for toxicity

-/-

2.11.4 STEP 4: Exposure assessment – threshold of concern approach

-/-

2.11.5 STEP 5: Refined risk assessment

-/-

2.11.6 Overall conclusion

In the PEC_{GW} simulation with FOCUS_PELMO 4.4.3 the metabolite AMPA does not show a potential to exceed groundwater concentrations of 0.1 µg/L. Therefore no further consideration of metabolite AMPA is needed in the relevance assessment of groundwater metabolites.

2.12 Consideration of isomeric composition in the risk assessment

2.12.1 Identity and physical chemical properties

Such consideration is not needed. Different isomers of glyphosate do not exist.

2.12.2 Methods of analysis

Such consideration is not needed. Different isomers of glyphosate and N-acetylglyphosate do not exist.

2.12.3 Mammalian toxicity

Glyphosate is not relevant concerning its isomeric composition.

2.12.4 Operator and Worker exposure

Glyphosate is not relevant concerning its isomeric composition.

2.12.5 Residues and Consumer risk assessment

Glyphosate and its metabolites are not relevant concerning their isomeric composition.

2.12.6 Environmental fate

The common name glyphosate designates an isomeric pure compound. Hence, data to assess a possible different environmental fate of stable glyphosate isomers are not required and were not submitted.

2.12.7 Ecotoxicology

The common name glyphosate designates an isomeric pure compound. Hence, data to assess a possible different environmental fate of stable glyphosate isomers are not required and were not submitted.

2.13 Residue definitions

2.13.1 Definition of residues for exposure/risk assessment

Soil
Glyphosate and its metabolite AMPA are potentially relevant compounds due to their occurrence at significant levels > 10 % in soil degradation studies.

The ecotoxicity of AMPA to soil organisms is comparable to the toxicity of the parent compound.

Surface water and sediment
Glyphosate and its metabolites AMPA and HMPA are potentially relevant compounds for further risk assessment in surface water, following the criteria from the Guidance Document on Aquatic Ecotoxicology (2002) due to their occurrence at significant levels in water/ sediment studies. The metabolite AMPA was detected in water phase and sediment phase with > 10 %, whereas the metabolite HMPA was detected only in water phase with 10 %.

Regarding surface water monitoring across Europe, glyphosate has been analyzed in almost 75000 surface water samples from about 4000 sites (from 1993-2011) and was detected in 33 % of samples, with 23 % above 0.1 µg/L. The maximum concentrations of glyphosate acid found in surface water reached from 1.3 to 370 µg/L. The highest glyphosate values in surface water were detected in Sweden (370 µg/L), Ireland (186 µg/L) and Belgium (139 µg/L). The main metabolite AMPA has been analysed in about 56700 samples from nearly 3000 sites (1997-2011) and was detected in 54 % of samples, with 46 % above 0.1 µg/L and maximum concentrations reaching from 0.22 to > 200 µg/L (Horth, 2012, BVL no 2310291).

The toxicity of AMPA and HMPA to aquatic organisms is lower than the toxicity of the parent. These metabolites are not ecotoxicologically relevant for the aquatic environment.

Groundwater
Glyphosate and its metabolite AMPA are potentially relevant compounds due to their occurrence at significant levels > 10 % in soil degradation studies. For both compounds the modelled concentration in groundwater did not exceed the trigger of 0.1 µg/L.
Regarding groundwater monitoring across Europe (Horth, 2012, BVL no 2310291), glyphosate and AMPA have been increasingly analysed and occasionally detected. Glyphosate has been analyzed in 66662 samples from about 675 sites (1993-2010) and detected in 1 % of samples, with 0.64 % above 0.1 µg/L; AMPA has been analyzed in 51652 samples from 1345 sites (1993 - 2011) and detected in 2.6 % of samples, with 0.77 % above 0.1 µg/L. The highest numbers of glyphosate detections have been reported from Denmark (4.7 µg/L) and France (24 µg/L). Findings exceeding the limit concentration 0.1 µg/l have also been measured in groundwater aquifers in Austria, Ireland, The Netherlands and the UK. Detailed groundwater monitoring studies demonstrating that glyphosate (at least partly)

exceeded 0.1 µg/l are available from Italy (Calliera et al., 2011, BVL no 2310280), Germany (Schmidt and Reichert, 2006, BVL no 2310282), The Netherlands (Franke et al., 2010, BVL no 2310284), Sweden (Carter and Pepper, 2005, BVL no 2310285), France (Anonymous, 2012, BVL no 2310289) and Spain (Sanchís et al., 2012, BVL no 2537361).

The toxicity of AMPA to aquatic organisms is lower than the toxicity of the parent. AMPA is not ecotoxicologically relevant for the groundwater compartment.

Plant and animal commodities
Sum of glyphosate, AMPA, N-acetyl-glyphosate and N-acetyl-AMPA, all expressed as glyphosate equivalents.

2.13.2 Definition of residues for monitoring

Soil
Parent glyphosate, AMPA.

Surface water and sediment
Parent glyphosate, AMPA.

AMPA is proposed as relevant residue for monitoring following precautionary principles resulting from the frequent detections in surface waters and the widespread intended uses of glyphosate in almost all crops.

Groundwater
Parent glyphosate, AMPA.

AMPA is proposed as relevant residue for monitoring following precautionary principles resulting from the frequent detections in groundwater and surface waters, the possible groundwater contamination path via bank filtration and the widespread intended uses of glyphosate in almost all crops..

Air
No criteria for definition of a relevant residue in air are available. By default, the relevant residue for the air compartment is the active substance glyphosate.

Plant and animal commodities

Residue definition for monitoring purposes in sweet corn, lentils, oilseeds rape, soya beans and maize (non-tolerant and tolerant, all modifications):
Sum of glyphosate and N-acetyl-glyphosate, expressed as glyphosate equivalents

Residue definition for monitoring purposes in other plant commodities:
Glyphosate

Residue definition for monitoring purposes in animal commodities:
Sum of glyphosate and N-acetyl-glyphosate, expressed as glyphosate

Level 3

Glyphosate

SUMMARY AND CONSIDERATION WITH RESPECT TO THE APPROVAL CRITERIA OF REGULATION (EC) No 1107/2009

IDENTIFICATION OF DATA GAPS, PROPOSED CONDITIONS, RISK MANAGEMENT MEASURES, ISSUES THAT COULD NOT BE FINALISED AND CRITICAL AREAS OF CONCERN

PROPOSED DECISION

3 Proposed decision with respect to the application

3.1 Background to the proposed decision

3.1.1 Proposal on acceptability against the approval criteria – Article 4 and Annex II of Regulation (EC) No 1107/2009

3.1.1.1 Article 4				
		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.	X		See Level 2 above
3.1.1.2 Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted		X	
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.	X		The assessment of the relevance of certain impurities in the technical material and/or specification needs to be clarified. The requested information is considered to be confirmatory in nature. The submission of further information on analytical methods of residues is required in order to get a complete data base to enable an evaluation according to EU Guidance Document SANCO/825/00 rev. 8.1, 16/11/2010. The submission of further information on toxicology is required to increase confidence in the decision. The submission of further information on residues is required

				for formal reasons in order to use all available data for an appropriate risk assessment. The submission of a study assessing the effects of the active substance towards microorganisms and a study with the representative plant protection product MON 52276 assessing the effects on non-target plants is considered to be confirmatory in nature, as required to increase confidence in the decision.
3.1.1.3 Restrictions on approval				
		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.	X		Minimum degree of purity of the active substance: ≥ 950 g/kg
3.1.1.4 Criteria for the approval of an active substance				
Dossier				
		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	X		Sufficient data was submitted to establish the ADI and the AOEL. An ARfD is not considered necessary by the RMS. If, however, EFSA or individual MS would wish to set an ARfD and provide convincing arguments that such a reference dose was in fact needed, the existing huge database will certainly allow to derive an appropriate figure. No further data would have to be generated for this purpose.
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed).	X		Sufficient data to derive residue definition in plant and animal commodities. Representative uses supported with sufficient supervised field trial data. No dietary intake concern. For desiccation of oilseeds (linseed, rapeseed, mustard seed) supervised field trial data were not sufficient for an evaluation.

Proposal on acceptability against the approval criteria

	In particular it is considered that the dossier: (a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.			
	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.	X		
Efficacy				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	X		Glyphosate is highly effective against the majority of annual and perennial mono- and dicotyledonous weeds. Herbicides containing glyphosate are used in agriculture as foliar sprays, at post-emergence of weeds in a wide range of arable crops (seeded and transplanted) to control a broad spectrum of weeds. The renewal submission only involves a selection of representative crop-related uses covering the majority of the

				volumes applied. Uses in the representative GAP include applications at pre-planting, post-planting but pre-emergence of crops and post-harvesting of all crops. Pre-harvest uses in cereals, oilseeds and pulses are for desiccation and annual and perennial weed control. Other uses include annual and perennial weed control in orchard crops and vines including olives, citrus fruits and nuts and for grassland renovation. Herbicides containing glyphosate are used at different rates in the EU in agriculture, horticulture, viticulture, forestry, orchards, plantation crops, amenities, home gardening, greenhouses, on aquatic areas, on hard surface areas, on railways, along roads, and on non-cultivated areas. According to the listed uses the application rate ranged from 0.72 to 2.88 kg as/ha. The application rate varies across the EU depending on the type and time of application and also on the weed species which are present on the treated area, weed growth stages or the crops which should be managed. Because of the uptake through the leaves, the best efficacy can be achieved if the application is on well developed foliage and especially for perennial weeds, in a period with sugar translocation to roots or other underground parts. One application per growing season is normally used and the weed plants treated at the recommended rate will not start growing again. Symptoms will be seen after 10 to 14 days after application.

Proposal on acceptability against the approval criteria

Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	X		Refer to Volume 3, chapters B.6, B.8 and B.9.
Composition				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	X		Refer to Volume 1, Level 2 and Volume 4.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	X		Open
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted			
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly	X		Sufficent analytical methods are available

Proposal on acceptability against the approval criteria

	calibrated, accurate and precise.			
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.		X	The following data gaps are identified: 1. A confirmatory method for glyphosate in animal fat and kidney/liver. 2. A confirmatory method for N-acetyl-glyphosate in dry plant materials and those with high water and high fat content. 3. A confirmatory method for N-acetyl-glyphosate in all kinds of animal matrices.
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		
Impact on human health				
Impact on human health - ADI, AOEL, ARfD				
		Yes	No	
	It is confirmed that (where relevant) an ADI, AOEL and ARfD can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.	X		Both the ADI and AOEL were derived from the overall NOAEL for maternal and developmental toxicity in the rabbit that was set at 50 mg/kg bw/day. The (pregnant) rabbit proved more vulnerable than other species. This NOAEL is lower than those obtained in the long-term studies in rodents or in short-term studies in rodents or dogs. When the usual assessment factor of 100 is applied, the resulting ADI is 0.5 mg/kg bw. For AOEL setting, the low oral absorption of approximately 20% must be taken into account for correction. Thus, a systemic AOEL of 0.1 mg/kg bw/day is proposed. An ARfD for glyphosate is not warranted because this substance is of low acute toxicity and because there is no evidence that a single dose would be sufficient to induce toxic

				effects that were observed in studies with repeated administration.
Impact on human health – proposed genotoxicity classification				
		Yes	No	
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as mutagen category 1A or 1B.**		X	No, glyphosate is devoid of a genotoxic potential (see 2.6.4).
Impact on human health – proposed carcinogenicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as carcinogen category 1A or 1B.**		X	No, classification and labelling for carcinogenicity is not warranted. This is based on a large number of long-term studies in rats did not reveal any evidence of carcinogenicity. In the mouse, a higher incidence of malignant lymphoma was observed in one out of five carcinogencity studies at an exaggerated dose level in a strain with high background incidence of this tumour type. See section 2.6.5 for justification that classification is not needed. Epidemiological studies in the whole did not provide evidence of carcinogenicity in man.

Proposal on acceptability against the approval criteria

ii)	Linked to above classification proposal. As became evident from exposure estimations exposure of humans towards the active substance, safener or synergist in MON 52276, under realistic proposed conditions of use, is not negligible irrespective of which toxicological endpoint is concerned.			
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**		X	In various two-generation studies in rats, there was no impact on fertility or reproductive performance (see 2.6.6). No classification and labelling for this endpoint is needed.
ii)	Linked to above classification proposal. As became evident from exposure estimations exposure of humans towards the active substance, safener or synergist in MON 52276, under realistic proposed conditions of use, is not negligible irrespective of which toxicological endpoint is concerned.			

Proposal on acceptability against the approval criteria

Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties**		X	See above. No classification for carcinogenicity or reproductive toxicity is proposed.
ii)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **toxic for reproduction category 2 and** in addition the RMS considers the substance **has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties**		X	No toxic effects on hormone producing or directly horomone-dependant organs have been noted in the huge number of toxicological studies.
iii)	Linked to either i) or ii) immediately above. As became evident from exposure estimations exposure of humans towards the active substance, safener or synergist in MON 52276, under realistic proposed conditions of use, is not negligible irrespective of which toxicological endpoint is concerned.			

Proposal on acceptability against the approval criteria

Fate and behaviour in the environment			
Persistent organic pollutant (POP)			
	Yes	No	
It is considered that the active substance **FULFILS** the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		X	On consideration of all available data on the characteristic of glyphosate, the substance does not fulfil the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1. In particular, glyphosate fulfils the criteria for persistence[1)], but neither the criteria for for long-range transport potential[2)] nor for bioaccumulation[3)]. 1) On the basis of the maximum DT_{50} value in water/sediment studies (total system) of 301.2 days glyphosate fulfils the P criterion of POP and exceeds the trigger of both, water phase (60 days) and sediment phase (180 days). This approach represents a conservative assessment. Using the geometric mean DT_{50} value (total system) of 74.5 days (range DT_{50}: 13.8 - > 301.2 days) from five water/sediment systems the trigger value of 60 days for water would be exceeded, whereas the trigger of 180 days for sediment would not be exceeded. Because of the very rapid adsorption of glyphosate to the sediment phase the total geomean DT_{50} value of 74.5 days would be compared to the sediment trigger of 180 days. Therefore glyphosate would not fulfil the P criterion of POP on the basis of the geomean DT_{50} value. The maximum $DegT_{50}$ of un-normalised field dissipation studies of 116.4 days does not exceed the trigger value of 180 days for soil. The P-criterion is not fulfilled.

				In soil laboratory degradation studies, the maximum DT_{50} value of 133.8 days would not exceed the trigger value of 180 days for soil. Therefore, glyphosate would not fulfil the P-criterion of POP. This approach represents a conservative assessment. Using the geometric mean DT_{50} value of 18.7 days (range 3.6 - 133.8 days, n = 17) the trigger value of 180 days for soil would not be exceeded. The P criterion would also not be fulfilled. 2) The low vapour pressure of 1.31×10^{-5} Pa (25°C) and the calculated atmospheric half-life < 2 d indicate a low potential of glyphosate for long-range transport via air. 3) With a log $P_{o/w}$ < -3.2 glyphosate is not a lipophilic compound. No testing on bioconcentration in fish is legally required. but a bioconcentration study has been conducted with different aquatic organsism which achieved a bioconcentration factor max. 10, which is far below the Annex VI BCF trigger value of 1000. Bioaccumulation of glyphosate due to bioconcentration in fat tissues or exceedance of the BCF trigger value of 5000 are unlikely.
Persistent, bioaccumulative and toxic substance (PBT)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		X	On consideration of all available data on the characteristic of glyphosate, the substance does not fulfil the criteria of a persistent, bioaccumulative and toxic (PBT) as laid out in Regulation 1107/2009 Annex II Section 3.7.2. In particular, glyphosate fulfils the criteria for persistence[1)], but neither the criteria for bioaccumulation[2)] nor for (eco)toxicity[3)]. 1) On the basis of the maximum DT_{50} value in water/sediment studies (total system) of 301.2 days glyphosate fulfils the P criterion of PBT and exceeds the trigger of both, water and

				sediment phase. This approach represents a conservative assessment. Using the geometric mean DT_{50} value (total system) of 74.5 days (range DT_{50}: 13.8 - > 301.2 days) from five water/sediment systems the trigger value of 40 days for water would be exceeded and the trigger of 120 days for sediment would not be exceeded. Because of the very rapid adsorption of glyphosate to the sediment phase the total geomean DT_{50} value of 74.5 days would be compared to the sediment trigger of 120 days. Therefore, glyphosate would not fulfil the P criterion of PBT on the basis of the geomean DT_{50} value. The maximum $DegT_{50}$ of un-normalised field dissipation studies of 116.4 days does not exceed the trigger value of 120 days for soil. The P-criterion is not fulfilled in soil. In soil laboratory degradation studies the maximum DT_{50} value of 133.8 days would exceed the trigger value of 120 days for soil. Therefore, glyphosate would fulfil the P-criterion of PBT. This approach would represent a conservative assessment. Using the geometric mean DT_{50} value of 18.7 days (range 3.6 - 133.8 days, n = 17) the trigger value of 120 days for soil would not be exceeded. The P criterion would not be fulfilled. 2) With a log $P_{o/w}$ < -3.2 glyphosate is not a lipophilic compound. No testing on bioconcentration in fish is legally required. but a bioconcentration study has been conducted with different aquatic organsism which achieved a bioconcentration factor max. 10, which is far below the Annex VI BCF trigger value of 1000. Bioaccumulation of glyphosate due to bioconcentration in fat tissues or

				exceedance of the BCF trigger value of 5000 are unlikely. 3) The lowest available NOEC for aquatic organisms amounts to 1.0 mg/L and is thus above the pertinent trigger value of 0.01 mg/L.
Very persistent and very bioaccumulative substance (vPvB).				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		X	On consideration of all available data on the characteristic of glyphosate, the substance does not fulfil the criteria of a very persistent and very bioaccumulative (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3. In particular, glyphosate fulfils the criteria for persistence[1)], but not the criteria for bioaccumulation[2)]. 1) On the basis of the maximum DT_{50} value in water/sediment studies (total system) of 301.2 days glyphosate fulfils the P criterion of vPvB and exceeds the trigger of both, water (60 days) and sediment phase (180 days). This approach represents the conservative assessment. Using the geometric mean DT_{50} value (total system) of 74.5 days (range DT_{50}: 13.8 - > 301.2 days) from five water sediment systems the trigger value of 60 days for water would be exceeded, whereas the trigger of 180 days for sediment would not be exceeded. Because of the very rapid adsorption of glyphosate to the sediment phase the total geomean DT_{50} value of 74.5 days would be compared to the sediment trigger of 180 days. Therefore glyphosate would not fulfil the P criterion of vPvB on the basis of geomean DT_{50} value. The maximum $DegT_{50}$ of un-normalised field dissipation studies of 116.4 days does not exceed the trigger value of 180 days for soil. The P-criterion is not fulfilled.

				In soil laboratory degradation studies the maximum DT_{50} value of 133.8 days would not exceed the trigger value of 180 days for soil. Therefore, glyphosate would not fulfil the P-criterion of vPvB. This approach represents the conservative assessment. Using the geometric mean DT_{50} value of 18.7 days (range 3.6 - 133.8 days, n = 17) the trigger value of 180 days for soil would not be exceeded. The P criterion would also not be fulfilled. 2) With a log $P_{o/w} < -3.2$ glyphosate is not a lipophilic compound. No testing on bioconcentration in fish is legally required. but a bioconcentration study has been conducted with different aquatic organsism which achieved a bioconcentration factor max. 10, which is far below the Annex VI BCF trigger value of 1000. Bioaccumulation of glyphosate due to bioconcentration in fat tissues or exceedance of the BCF trigger value of 5000 are unlikely.
Ecotoxicology				
		Yes	No	
	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account the severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.	X		*Birds* The calculated TER values for the acute and long-term risk resulting from an exposure of birds to glyphosate reach the acceptability criteria TER ≥ 10 and TER ≥ 5 for acute and long-term effects, repectively. The results of the assessment indicate an acceptable risk for birds due to uptake of contaminated food in the representative uses/use scenarios. *Mammals* The calculated TER values for the acute and long-term risk resulting from an exposure of mammals to reach the accep-

Proposal on acceptability against the approval criteria

				tability criteria TER ≥10 and TER ≥5 for acute and long-term effects, repectively for the following representative uses/use scenarios: - " all crops", - "crop maturity in cereals" - "crop maturity in oilseed rape". For use in orchard crops (vines including citrus & tree nuts, intrarow & spot treatment) the calculated TER values for the long-term risk resulting from an exposure of mammals to glyphosate do not achieve the acceptability criteria TER ≥ 5 with the maximum application rates. Nevertheless, risk can be mitigated with a serial application of 3 times 1440 g a.s./ha. *Aquatic organisms* The risk for aquatic organisms is acceptable in the representative uses/use scenarios. *Arthropods* With regard to the endpoints from the extended laboratory tests regarding lethal and sublethal effects and the predicted rates of glyphosate in-field as well as off-field, all calculated HQ values remain below the acceptability criterion. The calculated HQ values show an acceptable risk for non-target arthropods due to the intended use of the lead formulation MON 52276 in the representative uses/use scenarios. *Soil macro and mesofauna* TER values were calculated for glyphosate and the metabolite AMPA for a worst-case scenario with a max.annual application

				rate of 4.32 kg/ha glyphosate. The results of the assessment indicate an acceptable acute and long-term risk for earthworms and soil macro-organisms other than earthworms due to the representative uses/use scenarios. *Soil microbes* For the active substance glyphosate effects on the nitrogen cycle test could not be assessed due to an invalid study according to OECD guideline 216. Nevertheless, based on laboratory testing with MON 52276, the Annex VI trigger value of ≥ 25% effects after 28 days was not exceeded at concentrations of 1× and 5× the max. recommended annual use rate for 4.32 kg a.s./ha. Therefore, the use of MON 52276 according to the proposed use pattern can be considered not to result in any unacceptable adverse effects for soil micro-organisms. *Non target plants* A study assessing the effects towards non-target plants is required for the representative product MON 52276, as the risk for non-target plants cannot be reliably predicted on the basis of the active substance. The preliminary risk assessment proposes adequate bufferstrips in order to protect non–target plants from spray drift in off-field. The following risk mitigation measures are proposed:

Proposal on acceptability against the approval criteria

Intended uses	Application rate (g a.s./ha)	Buffer strip (m)	Buffer strip (m) with 90% drift reduction
Orchard crops, vine including citrus and tree nuts	1 x 2880	5 m	-
	1 x 2160	5 m	-
	3 x 1440	5 m	-
All crops (all seeded and transplanted crops	2 × 2160	10 m	-
	2 × 1440	10 m	-
	1 × 1440	5 m	-
	1 × 1080	5 m	-
Cereals, Oilseeds (pre-harvest)	1 x 2160	trigger not reached	5 m
	1 × 1440	10 m	-
	1 × 1080	10 m	-
	1 x 720	5 m	-

Only for the intended use 'pre-harvest' in cereals and oilseeds with one application rate at 1 x 2160 g a.s./ha, the acceptability criteria is not met. The risk for non-target plants arising from this intended use are considered unacceptable without drift reduction. If 90 % drift reduction nozzles are used, acceptable risk is achieved in several scenarios at 1 m. For the cereals scenario with an application rate of max. 1 x 2160 g a.s/ha we propose both the use of 90 % drift reduction nozzles and a buffer of 5 m.

Sewage treatment

Measurements of the oxygen consumption of glyphosate acid in activated sludge resulted in EC_{50}-values of > 100 mg/L. Glyphosate acid did not exhibit any significant symptoms up to the highest test concentrations. Because glyphosate acid has shown a low bactericidal activity a risk to biological sewage treatment is not expected.

Proposal on acceptability against the approval criteria

	It is considered that, on the basis of the assessment of Community or internationally agreed test guidelines, the substance **HAS** endocrine disrupting properties that may cause adverse effects on non-target organisms.		X	
	Linked to the consideration of the endocrine properties immediately above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.			N/A
	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.	X		Risk assessment for other pollinators than bees (e.g. bumblee bees or solitary bees) will be performed as soon as the agreed guidance for the assessment is available on EU level.
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	X		Definition of the residue for plant commodities Residue definition for enforcement purposes in sweet corn, lentils, oilseeds rape, soya beans and maize (non-tolerant and tolerant, all modifications): sum of glyphosate and N-acetyl-glyphosate, expressed as glyphosate

Proposal on acceptability against the approval criteria

				Residue definition for enforcement purposes in other plant commodities: glyphosate Residue definition for dietary intake purposes in plant commodities: sum of glyphosate, AMPA, N-acetyl-glyphosate and N-acetyl-AMPA, all expressed as glyphosate equivalents (For the future generation of residue data N-acetly-glyphosate and N-acetyl-AMPA are only mandatory analytes in GAT-modified crops.) Definition of the residue for animal commodities Residue definition for enforcement purposes in animal commodities: sum of glyphosate and N-acetyl-glyphosate, expressed as glyphosate Residue definition for dietary intake purposes in animal commodities: sum of glyphosate, AMPA, N-acetyl-glyphosate and N-acetyl-AMPA, all expressed as glyphosate equivalents (For the calculation of the maximum dietary burden for the purpose of MRL setting, only glyphosate and N-acetyl-glyphosate need to considered, since the reformation of both analytes from AMPA or N-acetly-AMPA is unlikely).

Proposal on acceptability against the approval criteria

				Definition of residues for monitoring *Soil* Glyphosate, AMPA *Surface water and sediment* Glyphosate, AMPA, HMPA *Groundwater* Glyphosate, AMPA *Air* Not defined.
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		*Glyphosate* PEC_{GW} < 0.1 µg/L in all nine FOCUS scenarios - The risk for groundwater is acceptable with no limitations for all intended uses. *AMPA* PEC_{GW} < 0.1 µg/L in in all nine FOCUS scenarios - The risk for groundwater is acceptable with no limitations for all intended uses. *Overall conclusion* The risk for groundwater from the application of glyphosate is acceptable with no limitations for all intended uses.

3.1.2 Proposal - Candidate for substitution

Candidate for substitution				
		Yes	No	
	It is considered that the active substance shall be approved as a candidate for substitution		X	On consideration of all available data on the characteristic of glyphosate, the active substance does not fulfil two of the three criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2. In particular, glyphosate does fulfil the criteria for persistence, but neither for bioaccumulation nor for (eco)toxicity.

3.1.3 Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** In particular it is considered that the substance **should NOT be classified or proposed for classification** in accordance with Regulation (EC) No 1272/2008 as at least one of the following: — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. In addition it is considered that **the substance is NOT**: — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100, — is deemed to be an endocrine disrupter, or — has neurotoxic or immunotoxic effects.		X	According to CLP, corrosive effects and severe eye damage are no longer distinguished. Glyphosate has to be classified and labelled for severe eye irritation/damage (Cat. 1, H318). Therefore, it cannot be considered to be of low risk. Glyphosate is considered persistent in soil. The maximum DT_{50} value of unnormalised field dissipation studies of 116.4 days exceeds the trigger value of 60 days for soil.

3.1.4 List of studies to be generated, still ongoing or available but not evaluated

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going	Study on-going and anticipated date of completion	Study available but not peer-reviewed
3.1.4.1 Identity of the active substance or formulation				
3.1.4.2 Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
Spectra of relevant impurities	Not relevant			
3.1.4.3 Data on uses and efficacy				
3.1.4.4 Data on handling, storage, transport, packaging and labelling				
3.1.4.5 Methods of analysis				
A confirmatory method for glyphosate in animal fat and kidney/liver.	Relevant, basic data set for all active substances!			

A confirmatory method for *N*-acetyl-glyphosate in all kinds of plant materials and in all kinds of animal matrices.	Relevant, basic data set for all active substances!			
3.1.4.6 Toxicology and metabolism				
KIIA, 5.5:	In the carcinogenicity studies in mice by [redacted] (1997, ASB2012-11493, notifier: Arysta) and by [redacted] (2009, ASB2012-11492, notifier: Nufarm), a certain increase in the incidence of malignant lymphoma in high dose males (6/50 as compared to 2/50 in the control in the first and 5/51 vs. 0/51 in the second study) was noted. The differences did not gain statistical significance. However, for more reliable assessment, historical control data from the performing laboratories should be provided.			

Level 3 – List of studies to be generated, still ongoing or available but not evaluated

3.1.4.7 Residue data				
Metabolism in GAT-modified crops, metabolism in livestock animals with N-acetyl-glyphosate, hydrolysis stability of N-acetly-glyphosate and N-acetyl-AMPA	The introduction of GAT-modified crops influences the residue definition in plant and animal commodities.	The relevant studies were submitted to the EU for an import tolerance and evaluated by EFSA in 2009 (RMS DE). However, the applicant is no member of the current task force, thus these studies are no part of the dossier submitted. Since the GAT-modification provides crucial information for a harmonised definition of the residue, the data have to be taken into account in the RAR. It needs to be clarified, if reference to the 2009 EU-evaluation by EFSA is sufficient in this case or if accessability of the studies by the Task Force is required.		
3.1.4.8 Environmental fate and behaviour				
3.1.4.9 Ecotoxicology				
Submission of supplemental studies on acute and chronic toxicity of glyphosate to aquatic organisms cited by FAO specifications and evaluations (2000/2001) for glyphosate. Rationale: For aquatic toxicity additional end points are cited, which were not submitted with the supplementary dossier.	Relevant, basic data set for risk assessment. Studies might provide supportive evidence and might replace relevant end points for risk calculation.			

Level 3 – List of studies to be generated, still ongoing or available but not evaluated

Submission of a study according to OECD 216 with maximum predicted environmental concentration (PEC) and five times that concentration.	Relevant, basic data set for risk assessment. For the evaluation of the active substance glyphosate acid further data would have to be generated for the purpose of risk assessment. The submitted nitrogen cycle test is considered not valid according to OECD guideline 216.	A study assessing effects of the active substance towards microorganisms is required.		
Submission of a study with the representative plant protection product MON 5227 6 according to OECD 227 including *Lycopersicum esculentum*. The test shall provide the ER50 values of the plant protection product to non-target plants.	Relevant, basic data set for risk assessment. For the evaluation of the representative plant protection product MON 52276, the study submitted is not considered to be valid and acceptable.	A study assessing effects on non-target plants is required for the plant protection product, as the risk cannot be reliably predicted on the basis of the active substance data.		

3.1.5 Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) No 546/2011, and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

Area of the risk assessment that could not be finalised on the basis of the available data	Relevance in relation to representative use(s)
Assessment of the relevance of impurities in technical material and/or specification (besides impurities 2, 11, 20, 21)	*All uses*
Assessment of the toxicological equivalence of the tested materials with the specification.	*All uses*
Safe maximum levels for relevant impurities cannot be derived based on the currently available data.	*All uses*
Effects of the active substance towards microorganisms.	*All uses*
Effects of the plant protection product on non-target plants.	*All uses*
Biodiversity: Regarding effects on biodiversity including indirect effects via trophic interaction, no quantitative assessment methods are established. However, risks for non-target organisms, in particular farmland bird species, were identified based on the evaluation of existing field studies.	*All uses*

3.1.6 Critical areas of concern

An issue is listed as a critical area of concern:
(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or
(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

Critical area of concern identified	Relevance in relation to representative use(s)
Biodiversity: The use of gyphosate and other broadspectrum herbicides may affect populations of non-target terrestrial arthropod and vertebrate (especially farmland bird) species via trophic interactions. Member states should pay attention to such potential indirect effects. Depending on the agricultural and ecological conditions, Member States may consider adequate risk mitigation measures.	*All uses*

3.1.7 Overview table of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)

All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Representative use		All crops (Pre planting) All seeded or transplanted crops	All crops (Post planting/ pre emergence) All seeded or transplanted crops	Cereals (Pre-harvest) Wheat, rye, triticale	Cereals (Pre-harvest) Barley and oats	Oilseeds (Pre-harvest) Rapeseed, mustard seed, linseed	Orchard crops, vines, including citrus & tree nuts (Post-emergence of weeds)	Orchard crops, vines, including citrus & tree nuts (Post-emergence of weeds) ULV
Operator risk	Risk identified							
	Assessment not finalised							
Worker risk	Risk identified							
	Assessment not finalised							
Bystander risk	Risk identified							
	Assessment not finalised							
Consumer risk	Risk identified							
	Assessment not finalised							

Overview table of the concerns identified

Representative use		All crops (Pre planting) All seeded or transplanted crops	All crops (Post planting/ pre emergence) All seeded or transplanted crops	Cereals (Pre-harvest) Wheat, rye, triticale	Cereals (Pre-harvest) Barley and oats	Oilseeds (Pre-harvest) Rapeseed, mustard seed, linseed	Orchard crops, vines, including citrus & tree nuts (Post-emergence of weeds)	Orchard crops, vines, including citrus & tree nuts (Post-emergence of weeds) ULV
Risk to wild non target terrestrial vertebrates	Risk identified							
	Assessment not finalised							
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified							
	Assessment not finalised							
Risk to aquatic organisms	Risk identified							
	Assessment not finalised							
Groundwater exposure active substance	Legal parametric value breached							
	Assessment not finalised							
Groundwater exposure metabolites	Legal parametric value breached							
	Parametric value of 10µg/L[(a)] breached							

Overview table of the concerns identified

Representative use		All crops (Pre planting) All seeded or transplanted crops	All crops (Post planting/ pre emergence) All seeded or transplanted crops	Cereals (Pre-harvest) Wheat, rye, triticale	Cereals (Pre-harvest) Barley and oats	Oilseeds (Pre-harvest) Rapeseed, mustard seed, linseed	Orchard crops, vines, including citrus & tree nuts (Post-emergence of weeds)	Orchard crops, vines, including citrus & tree nuts (Post-emergence of weeds) ULV
	Assessment not finalised							
Comments/Remarks								

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.
(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

3.1.8 Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	Justification

3.1.9 Critical issues on which the Co-RMS did not agree with the assessment by the RMS

Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

Issue on which Co-RMS disagrees with RMS	Opinion of Co-RMS	Opinion of RMS
None		

3.2 Proposed decision

It is proposed that:

[redacted]

3.3 Rational for the conditions and restrictions to be associated with any approval or authorisation(s), as appropriate

3.3.1 Particular conditions proposed to be taken into account to manage the risks identified

Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)
[redacted]	

APPENDICES

Appendix 1 - Guidance documents used in this assessment

[List of Guidance documents used in the conduct of the evaluation and risk assessment.]

Appendix 2 - Reference list

List [in the conventional format] any references specifically cited in Volume 1 (i.e references to underpinning documents such as PPR-Panel Opinions, EFSA conclusions, national documents etc.).