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Toxicology of glyphosate, isoxaflutole, dicamba and possible combination effects

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1 Introduction

The EU Commission will decide shortly on the applications filed by Bayer CropScience and Monsanto for the authorisation of two types of genetically modified soybeans, both of which are resistant to a combination of two herbicides:

1) Glyphosate + Dicamba (MON87708 x MON89788, application filed by Monsanto, EFSA-GMO-NL-2012-108)

2) Glyphosate + Isoxaflutole (FG72, application filed by Bayer CropScience, EFSA-GMO-BE-2011-98).

Both of the above will be used in the cultivation of the soybeans. The harvested soybeans may contain multiple residues, metabolites and/or the "inert ingredients" contained in the commercial formulation of the herbicides.

In their Scientific Opinions on the approval of both soybean types, EFSA did not evaluate the possible combined effects of the two active ingredients in the two soybean varieties.

Cumulated or combined effects of chemicals can occur in different ways, mainly if the chemicals:

- have an effect on the same biological target (e.g. the liver)
- share the same mode of action (e.g. inhibitors of certain enzymes)
- have the same toxicological endpoint (e.g. leukemia)
- mutually influence the effects (e.g. one chemical changes the metabolism of another chemical)
- share a similar chemical structure.

However, possible combined effects are not evaluated during the authorisation process of pesticides. In the present analysis, the toxicological properties of glyphosate and its most important metabolites are compared with those of dicamba and with those of isoxaflutole.

In a recent glyphosate low-dose toxicity review, it is stated that "today it is not clear, if its toxicity is because of Glyphosate, an "inert ingredient" or the two combined" (Mesnage 2015). So for this analysis, important findings for commercial formulations of glyphosate are considered, which are marked as such ("GBH").

The toxicological data are derived from the authorities' Draft and Renewal Assessment Reports (DAR and RAR) and from freely available scientific literature gained from database research in PubMed[1]. The focus is on the effects on human health caused by the active ingredients. For this reason, only studies performed with human or mammalian test systems are considered. Epidemiological studies were not considered because in most cases exposure was not only to glyphosate. Possible combination effects according to the criteria list above are identified.

1 United States National Library of Medicine of the National Institutes of Health; http://www.ncbi.nlm.nih.gov/pubmed; Access on November 5th 2015

2 Toxicological Properties and combined effects

Glyphosate and Dicamba

Table 1 shows the toxicological properties of glyphosate and dicamba.

Table 1: Effects of glyphosate and its main metabolite AMPA and of dicamba and its main metabolites DCSA and DCGA. Coloured: Common endpoints/effects/mode of actions

Toxicity	Glyphosate	AMPA	Dicamba	DCSA / DCGA (or M1)
References (if not listed explicitly with the data)	RAR 2013	RAR 2013	EFSA 2008	EFSA 2013
Acute toxicity				
Rat oral LD50	> 2000 mg/kg	„very low“	1581 mg/kg	2641/1460 mg/kg
Skin sensitization	No	No	Non-sensitizer	
Short term toxicity				
Target / critical effect	Rat: Cellular alterations in parotid salivary glands; AP and ALAT activity ↑; Caecum: distention and mucosal atrophy. Dog: prostate and uterus atrophy; AP activity ↑;	Increased kidney weights; epithelial hyperplasia of bladder and renal pelvis;	Liver, blood, behaviour	
Lowest NO(A)EL oral	300-400 mg/kg rat; 182 mg/kg (dog)	263mg/kg/d (dog)	50 mg/kg/d	15 (90 d dogs) / 474 mg/kg/d (28d Rats)
Genotoxicity/Mutagenicity	Strong evidence (IARC 2015, p. 77) Not a genotoxic carcinogen	negative	Unlikely; Positive in different tests (Perocco 1990; Filkowski 2003; Gonzalez 2006 and 2009; Cenkci 2009)	No signs
Long term toxicity				
Target / critical effect	Oxidative stress;[2] Rat: AP and ALAT activity ↑; kidney papillary necrosis; prostatis and periodontal inflammation ↑; caecum: distention and weight ↑; focal basophilia of acinar sells of parotid gland. Mouse: Enlarged/firm thymus[3]; increase in mineral deposition in the brain; histological findings in liver and bladder; malignant lymphoma in high dose. Non Hodgkin Lymphoma, kidney, pancreas (IARC 2015)		Body weight gain	Prostate, nasal cavity, heart/n.a.

2 Glyphosate RAR Addendum, available under http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html; Download 04.11.2015

3 Common target organ: thymus: Decreased thymus weight by DCSA, see under ‘Reproductive Toxicity’

Toxicity	Glyphosate	AMPA	Dicamba	DCSA / DCGA (or M1)
Carcinogenicity	No evidence of carcinogenicity; IARC 2A: Probably carcinogenic to human (IARC 2015); tumors in liver, thyroid, kidney, pancreas.	"Not considered necessary"	Not likely	
			Group D--Not Classifiable as to human carcinogenicity (USEPA 2009)	
Lowest NOAEL (rats)	(60 mg/kg/d) 100 mg/kg/d (rats); 150 mg/kg/d (mouse)		99 mg/kg/d	49 mg/kg/d / n.a.
Reproductive toxicity				
Target / critical effect Reproduction	Rat: Cellular alterations of salivary glands; litter size ↓; Homogenisation resistant sperm count; caecum distention; delay in sexual maturation	Mean foetal weight ↓	Liver weight, parental toxic dose	Offspring: decreased relative thymus weight Parental: increased relative brain and kidney weight/ n.a.
Lowest NO(A)EL	(197 mkg/kg/d); 351 mg/kg/d	400 mg/kg/d	35 mg/kg/d	4/n.a.
Target / critical effect Development	Rat: Ossification ↓; skeletal anomalies; post implantation losses. Rabbit: Late embryonic death; post implantation losses; cardiac malformations (dilated heart); abortion; increase in embryo/foetal death, malformations.	Reduced body weight gain	Mortality, abortions, "clinical observations"; Skeletal defects (USEPA 1994)	Rabbit: decreased number viable foetuses, implantation sites, corpora lutea / clinical signs of toxicity / n.a.
Lowest NO(A)EL	300 mg/kg/d (rat) (20 mg/kg/d) 50 mg/kg/d (rabbit)	150 mg/kg/d	30 mg/kg/d	25/50 mg/kg/d
Neurotoxicity	No			
Acute rat NOAEL	1000 mg/kg		402 mg/kg/d	
Subchronic rat NOAEL	617 mg/kg/d			
Developmental rat NOAEL	Not needed since no indications for neurotoxicity			
Delayed	n/a "since not an OP ester"		"< 79 mg/kg" (DAR 2007, p.98)	
Endocrine disruption	Yes; also in human cell lines (Hokanson 2007 GBH; Gasnier 2009; Thongprakaisang 2013); Reviewed by Mesnage (2015)	n/a		
Immunotoxicity	Weak evidence (IARC 2015)			
Subacute Rat NOAEL	>1450 mg/kg/d, mice			
ADI	0,3 mg/kg bw (suggested by RMS: 0,5)		0,3 mg/kg/d	0,04 mg/kg/d / n.a.
ARfD	none		0,3 mg/kg	0,3 mg/kg / n.a.

Empty cells: No data found; GBH: Glyphosate based herbicide; ↓ decreased; ↑ increased

The toxicity evaluation of glyphosate in general

Currently, there is a great deal of intensive debate about the renewal of authorisation for glyphosate. The authority responsible for risk assessment in the Rapporteur Member State Germany, the Bundesinstitut für Risikobewertung (BfR), did not declare glyphosate to be carcinogenic, unlike the International Agency on the Research of Cancer (IARC), being the specialised cancer agency of the World Health Organisation (WHO), which declared it to be "probably carcinogenic to humans".
One key aspect in the discussion is whether glyphosate is also genotoxic in humans. Again, the IARC views this in the affirmative, whereas the BfR comes to the opposite conclusion. This is an evaluation with theoretically far-reaching consequences - according to the pesticide authorisation directive 1107/2009, genotoxic carcinogens in humans cannot be authorized (EU 2009).
In a recent addendum to their Glyphosate RAR[2], the BfR reviewed other studies that they had not considered so far, and also genotoxicity due to oxidative stress. Nevertheless, the authority maintained its evaluation that glyphosate is not carcinogenic and not genotoxic. EFSA also shares the view of the RMS that "Glyphosate is unlikely to be genotoxic or to pose a carcinogenic threat to humans." (EFSA 2015a). The European Commission will be making a decision on further authorisation for glyphosate in the very near future.
The author of this report strongly suspects that carcinogenicity and genotoxicity cannot be ruled out.
The pesticide authorisation directive 1107/2009 is based on the precautionary principle: "The precautionary principle should be applied"[4]. If this principle were to be properly applied it would mean that glyphosate must be regarded as carcinogenic and genotoxic. For evaluating possible combination effects with Glyphosate, these properties are taken into account in the current analysis.

Metabolites of glyphosate and dicamba

Glyphosate:
AMPA (aminomethylphosphonic acid): The extensive documentation for the toxicity of AMPA in the Draft Assessment Report (DAR) is no longer available on the EFSA website[5], but the Renewal Assessment Report (RAR 2013). The RAR only provides a short summary without study results for AMPA (see Table 1). Neither a long-term nor a carcinogenicity study was performed because they were considered to be "not necessary" (RAR 2013). A literature review in PubMed did not reveal any further results relevant for AMPA.
NAG (N-Acetyl-Glyphosate): This is a "new" metabolite that was found in genetically engineered soybeans after they had been treated with glyphosate. EFSA (2009) evaluated its toxicity as being "not higher than Glyphosate". Studies for long-term toxicity and reproduction were not available, but according to EFSA, "it is not expected that the metabolite can cause such effects, also taking into account chemical structure".
In a report by the WHO/FAO Joint Meeting on Pesticide Residues (JMPR), similar evaluations were concluded (JMPR 2011). According to the report, NAG showed low acute toxicity, low sub-chronic toxicity and a lack of genotoxicity. It was concluded, that N-acetyl-glyphosate was of no greater toxicological concern than the parent glyphosate.
A literature review in PubMed for NAG did not reveal any further relevant results.

4 Refer to item (8) of EU (2009)
5 http://dar.efsa.europa.eu/dar-web/provision

Dicamba:
According to EFSA, dicamba is not a residue in dicamba-tolerant soybeans, but its metabolites DCSA and DCGA (EFSA 2013) are.
According to the DAR (2007), dicamba was the major component in edible plant parts; metabolites were seen in amounts of <10%; dicamba itself was deemed the residue of toxicological concern (DAR 2007).
The main metabolite of dicamba is 5-OH Dicamba (405873) with a low acute toxicity (LD50 >2000 mg/kg) and is evaluated as being “unlikely genotoxic” and “not mutagenic”. Further toxicological investigations were not performed with 5-OH Dicamba (DAR 2007).
A literature review in PubMed for 5-OH Dicamba did not reveal any results.

Combination effects of glyphosate and dicamba and their metabolites
Additionally to the data summarised in Table 1, most of which originates from studies performed by the applicants, a database research was carried out for the combined effects of glyphosate and dicamba.
The scientific literature revealed that the combined effects of glyphosate and dicamba have hardly been investigated at all. Research in PubMed resulted in only 23 hits. Only one of those was relevant to the scope of this study: The influence on the efficiency of antibiotics from the commercial formulations of the two herbicides.
According to the data evaluated in this study, glyphosate and dicamba with their metabolites share the following common effects, endpoints or modes of action:

- Genotoxicity
- Increased number of dead foetuses (glyphosate and DCSA)
- Skeletal defects
- Altered thymus weight
- Reduced susceptibility to antibiotic drugs (GBH and DBH[6])

Genotoxicity
The studies evaluated in the Review Assessment Report (RAR) of dicamba in 2008 did not show any mutagenic or genotoxic effects (EFSA 2008). Literature research in the scientific literature published in PubMed revealed five studies showing the mutagenicity and genotoxicity of dicamba in different test systems, among them GLP-conform test methods in mammalian cells (Gonzalez 2009) and tests in human blood cells (Perocco 1990). Three of these five studies were not identified in the Review Assessment Report for dicamba in 2008.

Increased number of dead foetuses
For glyphosate, the increased number of dead foetuses is evaluated as not relevant by the Rapporteur Member State (RMS) since there was no clear dose relationship (RAR 2013).
For dicamba, in an EFSA report (2013), one study is listed showing an increased number of dead foetuses by the dicamba metabolite DCSA, but this effect is not mentioned in the derivation for the Acceptable Daily Intake (ADI).

Skeletal defects
Both the EU RAR 2013 and the USEPA (1994) mention the observation of skeletal defects.

Altered thymus weight:
The thymus gland produces T-Lymphocytes, which are of decisive importance for the immune response since they neutralise harmful cells or mediate allergic reactions on contact

6 Dicamba based herbicides

with an allergic substance. Changes in thymus weight are, therefore, a sign of immunotoxicity (Elmore 2006). On the other hand, for glyphosate, one study with mice is referenced for immunotoxicity in the RAR (2013) as showing no effect. According to IARC (2015), there is “weak evidence” for immunotoxicity. Literature research in PubMed neither revealed further relevant results for immunotoxicity in mammals, nor for glyphosate, dicamba or their metabolites.
The indications for combined immunotoxic effects of glyphosate and dicamba are weak. Further investigations, in particular on the effect on the thymus gland, should be performed.

Reduced susceptibility to antibiotic drugs

The effects of pesticides on the efficiency of therapeutic antibiotics are not tested in the pesticide authorisation process. In very recent experiments, it was shown for the first time that the susceptibility of bacteria to antibiotics can be changed upon simultaneous exposure to sub-lethal concentrations of herbicides (Kurenbach et al. 2015). Commercial preparations of both glyphosate and dicamba reduced susceptibility to Ciprofloxacin in two common species of bacteria. The concentration of herbicides needed to induce a detectable antibiotic response was lower than the label-specified herbicide application rate. The authors also found that the herbicide-induced antibiotic response was additive when chemicals that cause similar phenotypic changes were combined.
Glyphosate is one of the most frequently found pesticides in the aquatic environment (Schulte-Oehlmann et al. 2011), forming the basis for herbicide-induced responses of bacteria to antibiotics. The conclusion of the authors: “Testing each compound in isolation and only for severe effects on microbes, as is done during risk evaluations of herbicides, may underestimate its role in the emergence of antibiotic resistance phenotypes.” The conclusion of the authors underpins the need for extended studies to investigate the combination effects of chemicals on microorganisms, including over longer periods of time.

Glyphosate and Isoxaflutole

The toxicological properties of glyphosate and isoxaflutole are shown in Table 2.

Table 2: Effects of Glyphosate and its main metabolite AMPA and isoxaflutole. Coloured: Common endpoints/effects/modes of action

Toxicity	**Glyphosate**	**AMPA**	**Isoxaflutole**
Reference (if not listed explicitly)	RAR 2013	RAR 2013	EU COM 2003
Acute toxicity			
Rat oral LD50	> 2000 mg/kg	„very low“	> 5000 mg/kg
Skin sensitization	No skin sensitizer	No	not classified
Short term toxicity			
Target / critical effect	Rat: Cellular alterations in parotid salivary glands (Ohrspeicheldrüse); AP and ALAT activity ↑; Caecum (Blinddarm): distention and mucosal atrophy. Dog: prostate and uterus atrophy; AP activity ↑;	Increased kidney weights; epithelial hyperplasia of bladder and renal pelvis	Periacinar hypertrophy in liver, ocular lesions, haematological effects. Eye, liver and red blood cells (J)
Lowest NO(A)EL oral	300-400 mg/kg rat; 182 mg/kg (dog)	263mg/kg/d (dog)	3 mg/kg bw/d, rat
Genotoxicity/Mutagenicity	Strong evidence (IARC 2015, p. 77) Not a genotoxic carcinogen	negative	Negative; Unlikely (J)
Long term toxicity			
Target / critical effect	Oxidative stress[2] Rat: AP and ALAT activity ↑; indicating liver toxicity (Mesnage 2015) kidney papillary necrosis; prostatis and periodontal inflammation ↑; caecum: distention and weight ↑; focal basophilia of acinar sells of parotid gland. Mouse: Enlarged/firm thymus; increase in mineral deposition in the brain; histological findings in liver and bladder; malignant lymphoma in high dose. Non Hodgkin Lymphoma, kidney, pancreas (IARC 2015)		Liver and thyroid effects; Liver, thyroid, ocular and nervous system (sciatic nerve axonal/myelin degeneration) effects (rat) (RAR); Increased liver weights and liver hystopathological findings (mice) (RAR);
Carcinogenicity	No evidence of carcinogenicity; IARC 2A: Probably carcinogenic to human (IARC 2015); tumors in liver, thyroid, kidney, pancreas.	“Not considered necessary”	Liver tumors; Thyroid tumors due to an imbalance of thyroid hormones. Carcinogenic in mice and rats (J); but “not relevant for humans” (RAR)
			Likely to be carcinogenic to humans (USEPA 2009)
Lowest NOAEL (rats)	(60 mg/kg/d) 100 mg/kg/d (rats); 150 mg/kg/d (mouse)		2 mg/kg/d (J)
Reproductive toxicity			
Target / critical effect Reproduction	Rat: Cellular alterations of salivary glands; litter size ↓; Homogenisation resistant sperm count; caecum distention; delay in sexual maturation	Mean foetal weight ↓	Reproductive effects (pup weight gain) at maternally toxic doses. Increased liver weight, liver hypertrophy and vacuolation

Toxicity	Glyphosate	AMPA	Isoxaflutole
			in parents. Decrease pup weight and pup viability. (RAR)
Lowest NO(A)EL	(197 mkg/kg/d); 351 mg/kg/d	400 mg/kg/d	2 mg/kg bw/d. 10 (rat) and 20 (rabbit) mg/kg/d (J)
Target / critical effect Development	Rat: Ossification ↓; skeletal anomalies; post implantation losses. Rabbit: Late embryonic death; post implantation loss; cardiac malformations (dilated heart); abortion; dead foetuses, malformations.	Reduced body weight gain	Rat oral, minor effects (delayed ossification)
Lowest NO(A)EL	300 mg/kg/d (rat) (20 mg/kg/d) 50 mg/kg/d (rabbit)	150 mg/kg/d	10 mg/kg bw/d, No teratogenic effects
Neurotoxicity	No		No (J)
Acute rat NOAEL	1000 mg/kg		2000 mg/kg bw (J)
Subchronic rat NOAEL	617 mg/kg/d		750 mg/kg/d (J)
Developmental rat NOAEL	Not needed since no indications for neurotoxicity		25 mg/kg/d (J); 250 mg/kg/d (RAR)
Delayed	No "since not an OP ester"		No relevant effects. Not relevant for this class of chemical substances (RAR)
Endocrine disruption	Yes; also in human cell lines (Hokanson 2007 GBH; Gasnier 2009; Thongprakaisang 2013); Reviewed by Mesnage (2015)		"No evidence" (RAR)
Immunotoxicity	Weak evidence (IARC 2015)		
Subacute NOAEL	>1450 mg/kg/d, mice		>279 mg/kg/d, rat (RAR)
ADI	0,3 mg/kg bw		0.02 mg/kg bw
ARfD	none		0,1 mg/kg (RAR)

Empty cells: No data found; J: JMPR 2013; RAR: RAR 2015; GBH: Glyphosate based herbicide; ↓ decreased; ↑ increased

Toxicity of isoxaflutole in general

The literature research for isoxaflutole in PubMed resulted in only 44 hits, suggesting that isoxaflutole is very poorly investigated in free literature. Nearly all the findings are based on studies performed by Industry.

Metabolites

Isoxaflutole (JMPR 2013):
RPA 202248: Acute and mutagenicity tests showed no higher toxicity than the parent compound.
RPA 203328: Acute, short term, mutagenicity and reproduction tests showed no higher toxicity than the parent compound
RPA 202248, RPA 205834 and RPA 207048 were not evaluated as considerable.

Combination effects of glyphosate and isoxaflutole and their metabolites

According to the data summarised in Table 2, glyphosate, isoxaflutole and their metabolites share the following common effects, endpoints or modes of action:

- Effects on the liver
- Tumours in liver and thyroid
- Teratogenic effects (Reduced ossification of embryos)

3 Conclusion

The present analysis of the toxicity data for glyphosate, dicamba and isoxaflutole shows the combined effects of glyphosate with both dicamba and isoxaflutole. These effects are, with dicamba, genotoxicity, an increased number of dead foetuses, altered thymus weight and, for GBH and DBH, reduced susceptibility to antibiotic drugs. With isoxaflutole, the combined effects identified were liver toxicity, tumours in liver and thyroid and teratogenic effects. Consumers can be exposed to a combination of these substances if they are found together as residues in soybeans or other food.

Combined effects are neither assessed within the European pesticide authorisation process nor during the authorisation process for the two varieties of genetically modified soybeans under scrutiny.

Furthermore, pesticide active ingredients such as glyphosate, dicamba and isoxaflutole are never applied alone, but always in their commercial formulations. These formulations are not tested extensively for authorisation. As mentioned in the introduction, at least for low dose effects it is currently not clear whether the effects of glyphosate derive from glyphosate alone or from inert ingredients or both of these together. For one group of ingredients in glyphosate-based herbicides (GBH), the tallow amines, “a higher toxicity was observed on all endpoints investigated compared to glyphosate” (EFSA 2015b). EFSA also mentions the synergistic effects of glyphosate and tallow amines concluding that: “The hypothesis of a possible synergistic toxicity between glyphosate and tallowamine co-formulant could not be verified. Dose additivity may be expected, at least regarding the irritation potential of the mixture to the eyes and possibly mucosal tissues as both compounds share these irritation properties. The genotoxicity, long-term toxicity and carcinogenicity, reproductive/ developmental toxicity and endocrine disrupting potential of POE-tallowamine should be further clarified. There is no information regarding the residues in plants and livestock”.

Based on the combination effects of the active ingredients identified in this analysis, it is strongly recommended that further specific investigations are carried out in this respect before authorising products, which may contain combined residues of the abovementioned herbicides. This should also include the commercial formulations and analyses of residues.

4 Abbreviations

NO(A)EL	No observed (adverse) effect level
LD50	Dose for lethality of 50% of the test objects
ADI	Acceptable Daily Intake
ARfD	Acute Reference Dose
GBH	Glyphosate based herbicides
DBH	Dicamba based herbicides

5 Literature

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