Pesticide Action Network Europe

Carcinogens in our food.

Pesticide metabolites with (un)known carcinogenic potential end up in our food

Background

EU policy provides that people are not exposed to carcinogens[1]. This means that alleged 'safe levels of exposure' (thresholds) shall not be applied to carcinogens and any exposure to these chemicals prevented. The industry sector has been attacking EU's policy on carcinogens for decades as one of their major lobby campaigns and has been promoting time and again the introduction of 'safe' thresholds.

European Food Safety Authority (EFSA) is the one that is developing guidelines for risk assessment of pesticides that need to give the final judgement on how to handle chemicals and this is also the case for the risk assessment of carcinogens[2]. No surprise EFSA's work has attracted great attention of industry. EFSA panels (where the guidelines are developed) functioned as a magnet for the industry and industry-linked experts that tried to get a seat in panels and working groups[3]. Conveniently for the industry, EFSA didn't maintain a conflict of interest policy during many years after its existence in 2004. Only because of intervention by the European Parliament a conflict-of-interest policy at EFSA was adopted but far from sufficient[4]. Currently, still half of the experts in EFSA panels have financial conflicts of interest[5]. A revolving door between EFSA staff and commercial bodies[6] also didn't help creating independence. EFSA further damaged its independence by organising joint 'invitation-only' meetings with industry lobby group ILSI; one in 2005 on genotoxic carcinogens[7] to conclude that actually safe levels do exist no

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[1] Regulation 1107/2009, Annex II, 3.6.3 for carcinogens category 1A/1B except for negligible exposure (this is excluding contact with humans)

[2] EFSA (European Food Safety Authority), 2012. Statement on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Journal 2012;10(3):2578, 5 pp. doi:10.2903/j.efsa.2012.2578

[3] PAN E report on TTC

[4] http://www.pan-europe.info/press-releases/2012/11/10-years-efsa-10-years-blind-love-industry

[5] https://corporateeurope.org/pressreleases/2017/06/nearly-half-experts-european-food-safety-authority-have-financial-conflicts

[6] http://www.foodnavigator.com/Policy/EFSA-comes-under-fire-for-latest-revolving-door-industry-recruitment

[7] S. Barlow, A.G. Renwick, J. Kleiner, J.W. Bridges, L. Busk, E. Dybing L. Edler,, G. Eisenbrand, J. Fink-Gremmels, A. Knaap, R. Kroes, D. Liem, D.J.G. Mu¨ller,

matter EU policy, and one in 2011 on TTC[8], the Threshold of Toxicological Concern, a safe threshold itself. The meetings were flooded with industry experts (and the animal welfare group EPAA), while all other stakeholders were excluded.

This long history of cosy relations between regulators and industry and bypassing other stakeholders triggered the Pesticide Action Network to closely follow decisions on carcinogenic pesticides. We took a sample of recent Commission decisions from Eurlex for the cases where carcinogenic pesticides or carcinogenic metabolites of pesticides are involved and evaluated the EU decisions taken. While pesticide active substances need to be tested for carcinogenicity, there was no such clear obligation for pesticide metabolites, isomers, impurities etc. (including formulants) for testing[9]. The obligation is to submit any information on potentially harmful effects and to test on a case-to-case basis. Industry generally didn't deliver much experimental data and limited itself to reasoning, creating numerous data gaps for metabolites and impurities.
No pesticides with classification C1A have been proposed by industry for market access and only one C1B (Maleic Hydrazide that is just approved); several pesticides are classified C2, suspected carcinogen. For metabolites and impurities EU Commission up to now failed to look at the carcinogenic potential. Metabolites and impurities are therefore at the centre of this evaluation.

Outcome evaluation Pesticide Action Network.
We evaluated 12 decisions with potential carcinogens and concluded that:

- People have been exposed to most of these active substances/metabolites for decades while the carcinogenic potential of metabolites and impurities was not assessed by EU Commission. These potential carcinogens can be found in food and in groundwater.
- In almost all cases the carcinogenic potential of a metabolite or impurity is not known (unknown classification, 1 A/B, 2 or not a carcinogen) and still the pesticide is (and has been) approved and consumers have potentially been exposed to carcinogens;
- Even now, after many years of market access, industry failed to submit solid information on the carcinogenic potential of metabolites and impurities
- C2 pesticides (Carfentrazone-ethyl, Iprovailcarb), suspected carcinogens, get no special treatment. They are treated as any other chemical, by traditional risk assessment with safe thresholds;
- Even the 1B pesticides (substances presumed to have carcinogenic potential for humans) like classified genotoxic carcinogen Hydrazine is approved by traditional risk assessment, clearly violating Regulation1107/2009
- For the potential carcinogens AMBA (metabolite from Mesotrione) residues could be found in animals fed with GM soybeans, as is the case for IN-A4098 (metabolite from Metsulfuron and other Triazines) in consumption meat;

S. Page, V. Rolland, J. Schlatter, A. Tritscher, W. Tueting, G. Wu¨rtzen, Risk assessment of substances that are both genotoxic and carcinogenic. Report of an International Conference organized by EFSA and WHO with support of ILSI Europe, Food and Chemical Toxicology 44 (2006) 1636–1650

[8] Workshop on the Threshold of Toxicological Concern: Scientific challenges and approaches. Organised by CEFIC, EU, EFSA, ILSI, EPAA, ISRTP, 8 – 10 June 2011 Brussels (Belgium)

[9] COMMISSION REGULATION (EU) No 283/2013 , of 1 March 2013

- The applicants (the industry) is given the permission (on a routine basis) to carry out additional tests and provide the results at a later stage without blocking the authorization of its products (almost all studied pesticides Carfentrazone, Thifensulfuron, Mesotrione, Flazasulfuron, Metsulfuron, Iprovalicarb).
- If a carcinogen gets in groundwater, it is only considered 'relevant' for assessment when it exceeds the groundwater standard of 0,1 µg/L (Carfentrazon, Thifensulfuron, Metsulfuron). If the pollution with the metabolite is above the groundwater standard, it can (and will in many cases) be qualified 'irrelevant' in a second tier assessment, using the TTC-threshold of 0,75 µg/L, another 'safe' level (designed by industry) or even up to 10 µg/L with an adequate 'consumer risk assessment'.

Recommendations.
This Pesticide Action Network study on carcinogens illustrates that the precautionary principle is completely ignored by EU Commission as is the high level of protection of EU groundwater bodies. If a carcinogenic potential of a substance is unknown, a pesticide must not get market access until solid experimental tests on the carcinogenic potential and classification are available.
The policy to allow potential carcinogenic pesticides on the market and allow industry to submit 'information' at a later stage should be stopped immediately. This violates the precautionary principle and doesn't guarantee the high level of protection from Regulation 1107/2009.

All that is left from the precautionary principle is words

Evaluation pesticide decisions.

Pesticide name	Carcinogenic substance	Adverse effects observed	EFSA opinion	COM decision	EU citizens exposed to carcinogens?
Carfentrazone-ethyl , herbicide classified C2 by EFSA	Carfentrazone-ethyl	Thymoma	Drinking water limit exceeded by 4 metabolites while carcinogenic potential cannot be excluded	Approval with confirmatory data request for carcinogenic potential metabolites; the pesticide is on the	In groundwater in some cases (winter cereals) above legal standard.. In food generally at level of detection (0,01 - 005 ppm)

				market for decades already	
Maleic hydrazide	Hydrazine (impurity); Metabolite 3-pyridazinone of unknown potential	Classified carcinogen 1B and genotoxic	EFSA considers Hydrazine non-genotoxic at level of 0,028 ppm (threshold approach), a no observed effect level in a genotoxicity study	Approval. On the market for decades	Maleic hydrazide, by residues in food (potatoes, carrots, eggs, milk) and likely doesn't exceed the groundwater standard. No information on environmental fate of Hydrazine
Thifensulfuron-methyl	Thifensulfuron-methyl and possibly the metabolite IN-A4098	Mammary tumours in rat studies	A LOAEL of 26 ppm was set, and because of a chronic NOAEL of 1,3 ppm, classification for carcinogenicity not considered necessary	Approval ("confirmatory data" procedure: applicant can deliver information on carcinogenicity at a later stage). On the market for decades.	Yes, by residues in food and drinking water; exceeds groundwater standard for pesticide and several of its metabolites; some possibly carcinogenic
Mesotrione	AMBA, metabolite	AMBA positive in in-vitro cytogenetic test and in vivo genotoxicity test	Genotoxic potential of AMBA needs to be clarified	Approval ("confirmatory data" procedure: applicant can deliver information on carcinogenicity at a later stage). On the market for decades.	Yes, by residues in food (animal origin, especially fed with genetically modified soy beans.
Flazasulfuron	Metabolites in humans, DMPU and HTPU, HTMU	Positive results obtained in the in vitro chromosome aberration test	Data gaps metabolites; need to clarify the genotoxic potential of DMPU and HTPU further in vitro tests; in vivo investigations needed for HTMU (groundwater pollutant) to see if the positive results can be overruled	Approved in 2004 (revision in 2018) On the market for decades.	Residues formed in humans by consumption of Flazasulfuron. Also residues in plants with unknown genotoxic potential (HTPP). Residues in groundwater

					water (attempt to classify irrelevant)
Metsulfuron-methyl	Genotoxic potential (plant) metabolite IN-A4098 (triazine amine) and IN-B5685	IN-A4098 'equivocal' (pos.?) results in *in vitro* clastogenicity assays and gene mutation assay; IN-B5685 positive in a chrom. aberration assay *in vitro*	Data gap IN-A4098 because groundwater pollutant > 0,1 ug/L, additional modelling might classify IN-A4098 as "irrelevant" ; IN-B5685 no need to investigate because <0,1 ug/L in groundwater	Approved in 2016 with "confirmatory data", to "confirm" that (IN-A4098) is not genotoxic and not relevant for risk assessment . On the market for decades.	Yes, by residues (esp. IN-A4098 and others of food of animal origin) and groundwater water of Metsulfuron and metabolites no information.
Iprovalicarb	Iprovalicarb C2; metabolite PMPA carcinogenic potential not excluded	C2 because of several types of tumours in rats; metabolite no data	Use Iprovalicarb (C2) safe at NOEAL; additional in vitro testing metabolite to exclude genotoxic potential	Approved in 2016 with "confirmatory information" as regards the genotoxic potential of soil metabolite PMPA. On the market for decades.	Yes, by residues in food (grapes) for Iprovalicarb and metabolites, even potential uptake from soils in next year. PMPA exceed groundwater standard.
Halosulfuron-methyl	New active substance; still no information on potential genotoxicity metabolite Chlorosulfonamide	In vitro gene mutation test showed health concerns	Genotoxic potential considered an "issue that could not be finalised"	Approved in 2013 with CD: "data to clarify the potential genotoxic properties of chlorosulfonamide acid". On the market since 2013.	Halosulfuron not above detection limit in food but present in groundwater. Chlorosulfuron is analysed in plants and in groundwater (data gaps).
Metosulam	Metosulam is a carcinogen (no classification) Unknown genotoxic potential of an impurity	Renal tumours for Metosulam.	Limited evidence of a carcinogenic effect for Metosulam. No information of genotoxic potential for the impurity ('issue that could not be finalised').	Approved in 2011 by imposing a 'safe level' for the carcinogen Metosulam. CD for the impurity. On the market since	No residues in food of Metosulam above the detection limit. Impurity unknown.

				2010.	
Buprofezin	Known genotoxic metabolite (Anilin),.	Anilin classiified M2, C2	While EFSA uses a threshold approach (MOE), it also states that exposure is a a priori concern since a threshold for a genotoxic carcinogen cannot be assumed.	Risk exposure to anilin not acceptable; only use on non-edible crops allowed. Operator exposure acceptable. Not approved in 2008, approved in 2011.	Exposure operator, bystanders and residents to Buprofezin (and possibly anilin) accepted.
Diflubenzuron	Known genotoxicty of impurity and metabolite 4-Chloroanilin (PCA); unknown potential metabolite PCAA		EFSA concluded that potential exposure to PCA as a residue (i.e. either for consumers or for workers and bystanders/residents) should be considered a priori as a concern since a threshold for a genotoxic carcinogen cannot be assumed.	Risk exposure to PCA not acceptable; only use on non-edible crops allowed. Operator exposure acceptable. Approved in 2008.	Exposure operator, bystanders and residents to Diflubenzuron (and possibly PCA) accepted.
2,4-DB	Genotoxic potential of impurity and metabolite 2,4-DCP (dichlorophenol); presence Dioxin	Positive effects in in vitro tests	2,4-DCP in meat and milk.	Pending new decision. On the market for decades.	