Chronic oral exposure of adult honey bees to PPPs: sensitivity and impact analysis of EFSA Bee GD

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1. Introduction

In 2013 the European Food Safety Authority (EFSA) published a guidance document (GD) on the risk assessment of plant protection products on bees [1], which intended to provide guidance for notifiers and authorities in the context of the review of plant protection products (PPPs) and their active substances under Regulation (EC) 1107/2009 (EC 2009). An ECPA impact analysis [2] indicated that for the chronic risk assessment (RA) only 18% of all uses would pass for honey bees and 0% for non-*Apis* bees. This is due to over-conservative assumptions relating to exposure and trigger values.

Since 2013, a number of chronic oral toxicity studies with adult honey bees have been conducted with active substances and formulated products .

The first aim of this poster is to summarize these industry data and based on the obtained endpoints determine the pass rates for honey bees, bumble bees and solitary bees according to the Bee GD. Moreover, the results of three different alternative, more realistic but still conservative approaches, are presented: a modified EPPO 2010 approach (ECPA option 1), an LDD_0 approach (ECPA option 2) and a refined EFSA approach using compound specific trigger values (ECPA option 3) [3].

2. Methods and data sources

For the current analysis, experimental data from 130 active substances or formulated products were available, covering 46 fungicides (belonging to e.g. organophosphates, strobilurins, triazoles), 55 herbicides (e.g. amides, benzfuranes, sulfonylureas), 26 insecticides (e.g. carbamates, neonicotinoids, organophosphates, pyrethroids, including 3 insecticide metabolites), 2 plant growth regulators (PGRs) and 1 additive. Mixtures of fungicides & insecticides were attributed to insecticides as they drive the toxicity. Overall 214 uses were covered: 65 fungicide spray and solid uses, 90 herbicide spray uses, incl. 2 PGR and 1 additive uses and 59 insecticide spray and solid uses. Studies on the chronic oral toxicity were performed according to OECD TG 245 or its precursors. Descriptive statistics of the available LDD_{50} and NOEDD values were determined.

For the honey bee (HB) screening step and Tier 1 risk assessment (RA), 'exposure-toxicity-ratios' (ETRs) were calculated according to [1] for different scenarios, from which risk for being exposed to the 'treated crop' and 'weeds flowering in the field' were regarded as the most relevant. Calculations were done using the EFSA-tool, Version 3 (October 2015). As standardized test methods for non-*Apis* bees were not available, RA for bumblebees (BB) and solitary bees (SB) were conducted based on 1/10th of the HB endpoint as surrogate.

Alternative RA options for HB have been proposed by ECPA [3]. The first is based upon the EPPO method 170 for systemic substances. It calculates a TER rather than a ETR and uses more representative and realistic 30% sugar content in nectar and 90th percentile residue RUD values (see [1], ECPA option 1, trigger 5). The second uses the worst-case LDD_0 (available for 45% of all uses; for the remaining 55% the EFSA standard 1st tier RA for treated crops was followed), which is subtracted from the daily dose according to [1] and the LDD_{50} and calculates an ETR (ECPA option 2). The third option uses the EFSA screening step with individual triggers to ensure the protection goal is met, taking into account the sigmoidal character of dose-response relationships and the type of endpoint instead of a fixed trigger of 0.03 (ECPA option 3).

3. Findings

3.1 Descriptive statistics

- Fungicides and herbicides displayed similar median LDD_{50}-values, being at least 400 times higher compared to those of insecticides. Moreover, respective NOEDDs were between 400 (fungicides) and 1200 (herbicides) times higher (Tab. 1).
- 10th percentile LDD_{50} and NOEDD-values derived for insecticides were about 300 times lower compared to those for fungicides and 670 and 1550 times lower compared to those for herbicides, respectively.

3.2 Confirmation of impact analysis findings

- Screening RA: Low pass rates for HB for all fungicide and herbicide uses, very low ones for insecticide uses. Almost no passed uses for BB & SB using 1/10th of HB endpoints (Tab. 2) confirm the findings of the 2013 impact analysis.
- Tier 1 RA: Whereas for treated crop and weeds fungicide and herbicide uses displayed moderate pass rates for HB, those for insecticide uses were still very low. Pass rates for BB & SB in the treated crop RA were slightly higher compared to screening RA, but still very low; no BB and almost no SB passed the weed RA.

3.3 Risk assessment options to better identify potential high risk products

- Results in Table 3 are to be compared with the screening RA for HB in Table 2.
- Option 1 showed a clear discrimination between products with toxicity (insecticides) vs. non-toxic products (herbicides, most fungicides) for HB RA. Because this is based on the use of the NOEDD and a trigger of 5 the protection goal of negligible effects was met.
- Option 2 showed a similar discrimination for all types of PPPs compared to ECPA option 1 when all uses were considered, irrespectively of whether LDD_0 values were available (45% of all uses) or not. Taking only those studies into consideration for which a worst-case LDD_0 could have been identified pass rates for fungicides and herbicides were even higher.
- Option 3 indicated an improved level of discrimination over the EFSA screening step ensuring that the same level of protection is achieved for each product. Because it takes into account the true dose-effect relationship, more non-toxic products passed the RA, but toxic insecticides were still identified.

Table 1: Descriptive statistics of LDD_{50} / NOEDD from chronic adult studies

Parameter	LDD_{50} / NOEDD [µg a.s./bee/day] for							
	Fungicides		Herbicides*		Insecticides**		All types	
	LDD_{50}	NOEDD	LDD_{50}	NOEDD	LDD_{50}	NOEDD	LDD_{50}	NOEDD
Min	0.058	0.058	1.120	1.120	0.0007	0.0004	0.0007	0.0004
Max	291.0	291.0	228.5	199.2	48.12	25.40	291.0	291.0
Mean	57.22	45.79	55.30	44.24	4.059	2.119	45.78	36.38
Median	34.90	10.30	44.65	30.90	0.088	0.026	17.79	10.30
10th percent.	1.900	0.940	4.700	4.670	0.007	0.003	0.106	0.029

* including two PGRs and one additive; ** including insecticidal metabolites

Table 2: Pass rates of screening & Tier 1 RA for chronic oral exposure of adult bees

Type of PPP	Pass rates [%] for								
	screening RA			Tier 1 RA, TC[1]			Tier 1 RA, W[2]		
	HB	BB[3]	SB[3]	HB	BB[3]	SB[3]	HB	BB[3]	SB[3]
Fungicides	32.3	3.1	3.1	56.9	7.7	12.3	60.7	0.0	1.6
Herbicides & PGRs	31.1	0.0	0.0	75.0	6.8	12.5	57.8	0.0	4.4
Insecticides, incl. metabolites	6.8	0.0	0.0	18.6	1.7	3.4	13.2	0.0	0.0
Total	24.8	0.9	0.9	53.8	5.7	9.9	49.7	0.0	2.6

TC = treated crop; W = weeds; [1] data set reduced for herbicides to n=88 as under crop applications are not relevant for treated crop RA; [2] data set reduced for solid insecticide uses to n=4 as seed treatment uses are not relevant for weed RA but only granule; [3] endpoint deriving from acute chronic HB testing

Table 3: Pass rates in alternative RA approaches for HB

Type of PPP	Pass rates [%] for HB using		
	ECPA option 1 (based on EPPO)	**ECPA option 2** (LDD_0 approach)[1]	**ECPA option 3** (trigger approach)[2]
Fungicides	64.6	95.2 (64.6)	61.0
Herbicides & PGRs	72.2	92.5 (85.6)	74.1
Insecticides, incl. metabolites	23.7	20.0 (25.4)	13.7
Total	56.5	66.7 (62.6)	45.9

[1] for 45% of uses LDD_0 approach could have been followed; for remaining 1st tier RA for treated crops was done; values in front of brackets give pass rates where only LDD_0 was used; values in brackets give pass rates for all uses (RA based on LDD_0 & EFSA); [2] data sets reduced for sprayed fungicide and herbicide, insecticide uses to n=25, 59, 85 and 25 due to missing slopes

4. Summary and conclusions

- **Risk assessments using real data confirm that the chronic risk for adults is the key driver of honey bee risk according to the EFSA Bee GD as stated in the original impact analysis [2]. In contrast the majority of fungicides and herbicides passed the Tier 1 RA for larvae [4] and even pass rates for insecticides were not even worse.**
- **A more selective risk assessment can be achieved by applying the standard EPPO 2010 approach based on the use of NOEDD endpoints and more realistic exposure assumptions.**
- **The EFSA 2013 approach can be significantly improved by taking into account the type of endpoint (NOEDD or LDD_{50}) and the dose-response relationship in order to meet the proposed protection goal more accurately.**
- **Using HB endpoints for BB and SB screening and Tier 1 RA will lead to failed BB and SB chronic RA for almost all active substances and their products, as valid laboratory methods will not be available in the next future.**
- **Industry is committed to pursue dialog with regulatory authorities and EFSA to share our experience and data to help develop a workable way forward.**

[1] EFSA (2013): EFSA Guidance Document on the risk assessment of plant production products on bees (*Apis mellifera*, *Bombus* spp. and solitary bees) (published on July 04, 2013, updated on 04 July 2014). EFSA Journal 11(7): 3295.
[2] Alix, A., Miles, M. & G. Weyman (2013): Sensitivity and impact analysis of the risk assessment for honey bees, bumble bees and solitary bees based on the guidance of the European Food Safety Authority. – ECPA, unpublished report.
[3] ECPA (2017): Proposal for a protective and workable regulatory European bee risk assessment scheme based on the EFSA bee guidance and other new data and available approaches. Unpublished report.
[4] Becker, R., Lückmann, J., Miles, M. et al. (2018): Sensitivity of honey bee larvae to plant protection products and impact on EFSA bee guidance document. In Hazards of pesticides to bees, 13th International Symposium of the ICP-PR, Valencia, Spain 2017, ed. by Oomen, P. A .& J. Pistorius, Julius-Kuhn-Archiv 462: 69-71.

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