PAN Europe input on "Public consultation on the draft scientific report on the cumulative dietary risk characterisation of pesticides that have acute effects on the nervous system"

1.2 Input from Risk Managers and threshold for regulatory consideration

Lines 238-239

We regret to see that risk managers agreed on a MOET of 100. The threshold 100 is the typical uncertainty factor used to calculate ADI from NOAEL, 10 for animal-to-human and 10 for human-to-human variations. Nevertheless, studies have shown that this could be an underestimation, particularly for extrapolations of data from humans to humans. This factor does not take into account the vulnerable groups of our population, such as children, the elderly and patients under medical treatment. A higher error may occur when data are extrapolated from adult animal studies where animals do not reach aging, to infants, children or elderly. A higher factor would be expected for a dietary risk assessment where all population groups might be exposed to pesticides via food. Ideally a different factor should be applied for each study used to calculate each MOE or a truly conservative approach would be to apply altogether a higher threshold for MOET. [KEMI, 2003, HUMAN HEALTH RISK ASSESSMENT. Proposals for the use of assessment (uncertainty factors)]

246-252

Although a big part of the population is covered, infants and elderly, whose chemical metabolism is slower (leading to longer retention of chemicals) are not covered in the analysis. This should be addressed later in the uncertainty analysis.

259-262

PAN Europe regrets to see that the probabilistic approach has been adopted (see previous comments https://www.pan-europe.info/sites/pan-europe.info/files/201809_Briefing%20mixture%20toxicity.pdf) which incorporates several assumptions. Even by using conservative assumptions, when these are "corrected" the results are questionable.

2.2.1 Cumulative assessment groups (CAGs)

Unfortunately, the selection of the studies inevitably leads to misleading NOAELs (higher than real NOAELs). The data used for CAGs derive from DARs/RARs but some key studies, that use lower dose exposure and therefore would result in effects with lower NOAEL have been omitted (e.g. neurodevelopmental toxicity). Developmental neurotoxicity is a hazard that has been addressed only recently in pesticides risk assessment. The data requirements before 2013 were focusing on adult acute toxicity and therefore did not include specific tests to address neurotoxicity during vulnerable periods of life time. DTN is even missing from dossiers approved after 2013. These studies, even if scarce, should had been included

where available, and these data gaps should have a significant weight in the uncertainty analysis, since NOAELs tend to be much lower in DNT studies. For example, in the case of DNT studies for Chlorpyrifos, effects on brain morphology were observed at dose levels of 0.3 and 0.1 mg/kg/day [Mie et al, 2018]. Several other effects on the nervous system were excluded, even if reported, at lower NOAELs (e.g. neurophysiological effects). Further, behavioural tests assessing the effects of pesticides on the cognitive function should had been used were available. A consideration of these effects should be taken into account especially when taking place at lower NOAEL. A wider range of neurotoxic effects were selected in the 2012 report that seem to be missing here [Nielsen, E., Nørhede, P., Boberg, J., Isling, L. K., Kroghsbo, S., Hadrup, N., ... Larsen, J. C. (2012). Identification of Cumulative Assessment Groups of Pesticides. European Food Safety Authority.] Furthermore, the dossiers of some of the pesticides had data gaps, even for the selected studies. According to EFSA analysis on establishing CAGs for the nervous system, for many old substances even the neurotoxicity study for acute effects was not available. The report states "This absence of a neurotoxicity study may result in overestimated NOAELs for some ASs (and thus underestimating the actual risk) as information on some indicators is missing in this case".

Furthermore, peer reviewed scientific literature should had been revised to evaluate whether lower NOAELs have been reported, and identify further studies reporting neurotoxicity [also proposed by Nielsen et al, 2012]. Peer-reviewed literature could help to establish additional CAGs when data were not sufficient. Since the dossiers have data gaps the academic literature should had been consulted. It is incredible that peer reviewed literature was dismissed even when incorporated in the RARs/DARs. Not using the most recent studies to address nervous system toxicity makes the current assessment to be out of date.

2.2.2 Cumulative exposure assessments

See comments under paragraph 1.2.

Lines 315-316 and 329-330.

Both models are based on Monte Carlo simulation. It would be more interesting to compare two completely different models and evaluate the differences in the results.

2.2.2.4 There is no justification to exclude EFSA monitoring data that exceed MRLs. MRLs change all the time (with authorisation or following a review or request), and until the market adjusts to the new MRLs food items may contain residues above the new MRLs for some period resulting in human population being exposed to higher levels than the permitted ones. Since this is the reality there is no justification to exclude monitoring data that are above MRLs. These are official monitoring data from food that is consumed from the general public.

2.3.1. Identification of sources of uncertainty affecting the assessment

Uncertainties not included:

- The sources of data seem outdated to carry out an assessment "in the light of current scientific and technical knowledge" on the acute and chronic toxicity of the nervous system. This is particularly the case for pesticide dossiers submitted prior to Commission Regulation (EU) No 283/2013, which lack specific data to assess neurotoxicity, particularly in vulnerable population groups. Even some old dossiers appear to have data gaps. This will lead to higher NOAELs and overestimation of MOETs.
- Peer reviewed scientific literature was not used at all, even when included in the pesticide dossiers. Lower NOAELs have been reported in the scientific literature and these should be taken into account. According to Reg (EC) 1107/2009 Article 8(5), an assessment is not complete without including studies from the scientific peer-reviewed open literature.
- It is of concern the numerous articles in the open scientific literature that report the impact of pesticides, particularly insecticides in the brain development, where not addressed in the assessment. For example: Bellanger et al [J Clin Endocrinol Metab. 2015 Apr; 100(4): 1256–1266. doi: 10.1210/jc.2014-4323] have shown that exposure to endocrine disruptors in Europe contribute substantially to neurobehavioral deficits and disease, and organophosphate pesticides is one of the main drivers. A systematic review of 27 studies (Muñoz-Quezada et al, 2013) has shown that prenatal and early childhood exposures to organophosphate (OP) pesticides among children lead to neurodevelopmental effects such as cognitive deficits (memory loss), behavioural deficits and motor deficits [Neurotoxicology 2013;39:158-68. doi:10.1016/j.neuro.2013.09.003.]. Another review also demonstrates the neurotoxic impact of insecticide exposure during the period of cerebral development [Cassereau et al Curr Med Chem. 2017; 24(27):2988-3001. doi: 10.2174/0929867324666170526122654.].
- Human data were not included in the assessment, even when available. These usually involve lower exposures and would result in lower NOAELs.
- Studies from dossiers were not validated against raw data. Recent reports show that in many cases the reporting of the protocol studies is poor and adverse effects are often not reported [Mie et al Environ Health. 2018; 16;17(1):77. doi: 10.1186/s12940-018-0421-y for DNT; Peter Clausing 2019, Chronically underrated; Portier CJ, Armstrong BK, Baguley BC, et al Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)J Epidemiol Community Health 2016;70:741-745.].
- A MOET of 100 doesn't allow to take into account human to human differences (vulnerable groups of the population such as babies, toddlers, children and elderly, as well as people with diseases). When studies are extrapolated from adult animals the uncertainty factor could be much higher than 100 [KEMI, Human health risk assessment: Proposals for the use of assessment (uncertainty) factors 2003].

Considering all the uncertainties due to the use of old studies a MOET higher than 100 would be more appropriate.

- Metabolism in infants and elderly may be lower, leading to higher retention of chemicals in the system and therefore higher likelihood of toxic effects
- 422 AS were selected it is possible that other substances not incorporated in the assessment but detected in monitoring data could have effects on the nervous system
- Baseline exposure is assumed to be zero although all human population groups already have chemicals in their system due to previous exposures, these include pesticides and other chemicals (Human biomonitoring: facts and figures. Copenhagen: WHO Regional Office for Europe, 2015; HBM4EU: Scoping paper on the development of an indicator on chemical exposure in the European population Deliverable Report D 5.3 WP 5 – Translation of results into policy, 2017). The likelihood that these chemicals may contribute to the toxicity cannot be disregarded.
- People are also exposed to pesticides through other routes, particularly if they are residents of agricultural areas. Furthermore about 10% of pesticides are used in the pest management of public areas (parks, gardens, cemeteries and golf courses) and people use them in their private gardens. This non dietary exposure to pesticides is evident from studies showing that even people that eat organic food are exposed to pesticides. Therefore, the level of exposure is likely to be higher than the one estimated.
- Around 7% of the samples from the official monitoring programmes exceed the MRLs, these include the suspected samples that were excluded from the analysis. This means that a fraction of the food sold in EU market, particularly raw fruit and vegetables may have pesticide residues that exceed the EU MRLs. The official monitoring is not always 100% objective and differs from country to country; samples that exceed MRLs may be missed. A source of uncertainty is that unfortunately some fruit and vegetables will have residues that exceed the EU MRLs.

2.3.2. Model and process for characterising overall uncertainty

Children are more sensitive to exposure therefore, be more protective (Reg EC 1107/2009 calls for a high level of protection), children or toddlers should also be selected for the uncertainty assessment, even though the numbers were lower. Extrapolating from adults to children creates additional uncertainty. By selecting an adult population all the sources of uncertainty due to potential effects in infants, toddlers and children or the vulnerable groups of society are downplayed. Most of the studies collected are done in adult animals. Also, toddlers and small children will be exposed to fruit by grabbing the fruit and then putting then putting their fingers in their mouth or grabbing their food. The choice to carry out the uncertainty assessment in adults is already biased as several questions will be answered only focusing on adults (e.g. peeling of the fruit or data gaps in toxicity studies).

5. Conclusions

Addressing cumulative and synergistic effects of pesticide products and their residues it is a legal requirement that has not been implemented for 14 years now. Therefore, an assessment on the safety of these products taking into account mixture effects is urgent. Although we welcome EFSA's intention to develop CRA, we are very disappointed with the current procedure, particularly the numerous assumptions, the uncertainty analysis and the questionable conclusion. The overall uncertainty analysis appears completely biased to favour a result that wouldn't require any regulatory action to address mixture effects. The experts' judgement alters remarkably an already conservative exposure assessment (Tier II is less conservative than Tier I) with missing toxicity-related data and certain neurotoxicity endpoints (neurochemical effects other than AChE inhibition, behavioural or cognitive effects). The assessment has great limitations from the start because it excludes some of the most sensitive studies available not only from open scientific literature but even protocol studies such as the neurodevelopmental toxicity. Even with these limitations a risk (MOET<100) was identified in 8 populations for CAG-NAN and 6 populations for CAG-NAM, including all children and toddlers' populations in both CAGs. It is incredible that expert judgment results in 5 or 6 times higher MOETs. This uncertainty analysis seems to be a strategic approach to conclude on purpose that there is no human risk due to pesticide exposure. Dietary risk assessment has to be adapted to the worst-case scenario, where the most vulnerable groups of the population will be exposed to the highest number of pesticides possible that act on the nervous system. The uncertainty analysis should be repeated, using a precautionary approach, focusing on the vulnerable groups of the population, addressing the missing data and taking into consideration that pesticides are not the only pesticides we're exposed to and neither food is the only route of exposure (refer to additional sources of uncertainty in section 2.3.2). Moreover, one wonders why EFSA decided to examine acute neurotoxic effects of pesticides via food consumption even though it collected data addressing both chronic and acute neurotoxic effects. It seems that chronic neurotoxic effects would be more relevant if exposure takes place through food.