PAN Europe's input on "Public consultation on the draft scientific report on the cumulative dietary risk characterisation of pesticides that have chronic effects on the thyroid system"

2.2.1. Cumulative assessment groups (CAGs)

Lines 283-289. The hypothesis that hypothoroidism is a secondary effect is not supported by scientific evidence on the absence of thyroid hormone effects. The proposal of the CAG establishment is to ask for thyroid hormone levels rather than assessing it by expert knowledge elicitation (EKE) and Monte Carlo simulations. Concluding that out of the 114 substances (subtracting the 14 with known MoA) only 71 (median) actually produce an effect (removing 43 substances from the assessment), without scientific evidence that prove it, is of concern, particularly when these affects are seen at lower NOAELs.

Unfortunately, the selection of the studies inevitably leads to misleading NOAELs (higher than real NOAELs). As explained in the EFSA report (establishing CAGS), the current OECD test guidelines for repeated dose toxicological studies and TG 443 (extended one-generation reproductive toxicity study; OECD, 2011) that require measurements of thyroid hormone levels are not available for most of the compounds assessed. In fact, in standard guidelines for toxicological studies analysis of hormones such as T3, T4 and TSH were not a mandatory requirement for the DAR/RARs used in the assessment, which creates a major data gap. However, studies have shown that chemicals that disturb the level of T3 and T4 and/or bind to thyroid hormone receptors may also cause developmental effects, that have not been incorporated in this assessment. Not taking into account thyroid-mediated impaired neurodevelopment is a major weakness of the present study, since these effects occur at very low doses. Hence, the present pilot study is incomplete.

Furthermore, peer reviewed scientific literature has not been revised to identify further studies reporting thyroid toxicity beyond the DARs/RARs and evaluate whether these effects occur at lower NOAELs [also proposed DTU report (Nielsen et al, 2012)]. Peer-reviewed literature could help to establish additional CAGs when data are not sufficient. Assessing endocrine disrupting effects through the thyroid is a very recent data requirement (November 2018) and key studies are missing from the pesticide dossiers. Since the dossiers have data gaps the academic literature must be 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 thyroid system toxicity makes the current assessment to be out of date.

For example, Maranghi et al. [Food Chem Toxicol. 2013;59:261-71. doi: 10.1016/j.fct.2013.05.048] exposed Sprague Dawley dams to ETU (common metabolite of

dithiocarbamates such as maneb, mancozeb, and metiram and zineb) and F1 generation until sexual maturity and found thyroid hormone changes together with developmental effects in pups even at 0.1 mg/kg. This would lead to NOAEL below 0.1 mg/kg, which is much lower than the 0.4 mg/kg incorporated in the CAG analysis.

The missing data could lead to erroneous conclusions on the main risk drivers and on which compounds have the lower NOAELs.

2.2.2. Cumulative exposure assessments

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 (including infants and children) can be exposed to pesticides via food. Ideally a different factor should be applied for each pesticide/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)]

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.

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 when using, as described in the text, conservative assumptions, when these are “corrected” the results are questionable.

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.

2.2.2.1. Cumulative exposure assessment for CAG-TCF

Here the analysis has found some risk in toddlers. Considering that the most sensitive tests have not been used and that thyroid chronic effects are observed at much lower doses than the ones reported in the studies of DARs/RARs, the data imply that there is a risk, particularly for the most vulnerable ones. One could assume that these risks are also true for infants.

2.3.1

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 chronic toxicity of the thyroid system. Thyroid effects, particularly hormone levels were just option of the data requirement up to 2013 and several dossiers did not include these data. The extended one generation reproduction toxicity study was only included in the data requirements in 2018, with the endorsement of the endocrine criteria. Therefore thyroid-sensitive tests are missing from the dossiers. Not taking into account the most sensitive protocol studies leads to higher NOAELs, overestimation of MOETs and total underestimation of the risk from the cumulative effects of these pesticides.
- Peer reviewed scientific literature was not used at all to incorporate adverse effects, 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.
- Thyroid disruption may take place at lower doses that might not be predicted by effects seen at higher doses (non-monotonic response). Therefore, by excluding data when effects do not follow a linear response, will inevitably lead to excluding real toxic effects on thyroid and calculating a much higher NOAEL [Vandenberg et al Endocr Rev. 2012;33(3):378-455. doi: 10.1210/er.2011-1050].
- It is of concern the numerous articles in the open scientific literature that report the impact of pesticides, particularly insecticides in the thyroid, where not addressed in the assessment. For examplem Maranghi et al. [Food Chem Toxicol. 2013;59:261-71. doi: 10.1016/j.fct.2013.05.048] found thyroid mediated reproductive and developmental effects in rats at much lower LOAEL following oral ETU exposure, leading to lower NOAELs than the ones reported here.
- 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). This is particularly important for thyroid effects that may lead to developmental disorders in children. 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 thyroid 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). Organochlorpine pesticides, for example, which are still found in the environment and human populations have the capacity to disrupt the thyroid hormone system and may have accumulative effect with current exposures [Freire et al Environ Res. 2013;127:7-15. doi: 10.1016/j.envres.2013.09.001. Epub 2013 Oct 29.]
- 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 imported-food 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 instead of addressing the major data gaps in thyroid chronic toxicity assessment that should prevent to reach such conclusion. It seems to be a strategic approach to conclude on purpose that there is no human risk due to cumulative pesticide exposure. Thyroid-mediated developmental and neurodevelopmental effects cannot be excluded from the assessment, since these may take place at very low exposure levels. 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 thyroid system. We regret to conclude that without data on the effects during early development following low dose exposures, the current assessment is futile (and out of date).