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Brussels, the 4th of April 2013

Subject: **EFSA Scientific Opinion on the hazard assessment of endocrine substances.**

Dear Commissioner Borg,

We would like to share some reflections with you concerning the EFSA scientific opinion on Endocrine Substances which has been issued on the 20th of March.

The EFSA opinion should help to create sound scientific criteria according to Regulation 1107/2009 and the Biocide Regulation. We feel EFSA partly succeeded in this mission, while there are also questionable elements in the opinion that have no link to the pesticides well as biocide Regulation at all.

EAS as the regulatory category for pesticides and biocides.

The purpose of developing criteria cannot be misunderstood much. In fact it is clearly defined in the law: they are meant for pesticides and biocides with '*endocrine disrupting properties'.* So far the best description for chemicals with endocrine disrupting properties we have seen is the one from the Endocrine Society, the professional organisation of 40.000 endocrinologists worldwide who wrote: '*an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action*'[1]. EFSA however chooses to put forward another category, the endocrine active substances (EAS, page 11 of the opinion). While this could add to

[1] Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, Woodruff TJ and Vom Saal FS, 2012. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. Endocrinology, 153, 4097-4110.

confusion, the EFSA description is close to the one of the specialised scientists: '*any chemical that can interact directly or indirectly with the endocrine system, and subsequently result in an effect on the endocrine system, target organs and tissues*'[2]. While we prefer the description of the Endocrine Society, we may agree with the EFSA translation of endocrine disrupting properties into EAS.
Adverse effects indeed should not be part of the description as the Endocrine Society emphasizes in their statement: 'while it is critical for hazard identification to be able to capture the sensitivity of human and wildlife to chemicals that pose a potential risk, the ability of a chemical to interfere with hormone action (i.e. the hazard), is of itself a reliable predictor for adverse outcomes'. Thus professional scientists point out that hazard is enough for regulating, just as Regulation 1107/2009 requires. We therefore recommend you to promote EAS as the regulatory category for pesticides and biocides as defined on page 11 of the EFSA opinion; not with additional text as on page 15–and surely not endocrine disruptors as suggested by JRC- in future inter-services consultations with other DG's. PAN Europe believes that considerations on adverse effects should not be part of the criteria.

No place for 'endocrine disruptors' in the criteria for pesticides and biocides.
We do not understand the inclusion of text in the EFSA opinion on 'endocrine disruptors' as defined by WHO/IPCS. Going to section 3 of the EFSA opinion (page 15) a sudden move is made from EAS to ED (endocrine disruptors) without proper justification. Any connection to the pesticide/biocide Regulation with the WHO/IPCS ED-definition is lacking. The IPCS/WHO category requires a high burden of proof on mode-of-actions and causality which would change the pesticide legislation fundamentally. This part might be included for covering other chemical areas but for pesticides/biocides it is irrelevant. Given the remit of EFSA and the origin of the criteria, Regulation 1107/2009 text on 'endocrine disruptors' should be disregarded.

Data requirements for pesticides and biocides need to be adapted soon to cover the developmental phase.
A crucial positive element in the opinion is that EFSA SC states that in testing protocols on endocrines the critical points of exposure during development need to be covered. As you know in the current data requirements of pesticides (Annex II, 1107/2009) the OECD long-term testing protocols lack in-utero exposure and will likely miss many harmful effects. Therefore all pesticides allowed on the market are inadequately tested for this -probably- most crucial risk, the exposure in development with potentially irreversible effects at later life stages. We urge you to include testing protocols soon in the data requirements of pesticides covering this very important life stage and add testing protocols that cover all life stages. We also propose to start regulating pesticides already at the end of 2013 based on the data available in academic studies and current science.

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[2] EFSA Scientific Committee; Scientific Opinion on the hazard assessment of endocrine disruptors: scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. EFSA Journal 2013;11(3):3132. [84 pp.] doi: 10.2903/j.efsa.2013.3132. Available online: www.efsa.europa.eu/efsajournal

EFSA creates loopholes for industry to escape banning of pesticides and biocides.
The part of the opinion we do not like at all is the part on a causal relation between endocrine activity and adverse effect. While EAS clearly defines endocrine disrupting properties, the pesticide/biocide Regulation states that it is sufficient to ban these chemicals if they *'may' cause adverse effects*. There is nothing on a causal relation and we think EFSA is not mandated to add elements which are not part of the EU pesticide law. Laws made in co-decision between Parliament and Council should be respected at a lower level. Section 3 of the EFSA opinion therefore is not justified from a legal point of view.
On top of this, all elements mentioned by EFSA are designed to disqualify adverse effects seen in test animals and therefore serve a commercial concern (assumptions on being a false positive). While all attention is given to these allegedly 'false positives', attention is lacking for 'false negatives', the main concern of citizens. We regret this unbalance in attention of the EFSA working group.

Massive industry infiltration overlooked.
Taking a closer look at the 'tools' proposed to disqualify observed effects, we note that they are developed and promoted by chemical industry, generally by industry lobby club ILSI (International Life Science Institute). For instance, Section 3.3 describes such an industry invention, the 'human relevance' of effects observed in test animals. Using animal testing to protect people and trying to disqualify an undesired outcome is something what we can understand from industry but the fact that regulators embrace these inventions is quite astonishing. No independent scientist would even consider this type of tools. Any physiologist knows we have such a limited knowledge of the body response to chemicals that it would be largely speculation to describe the mode of action of a given chemical with a reasonable certainty in the body. An endocrine active chemical will trigger activity on cellular level, likely indirect action by G-protein, likely translation by DNA in proteins, possible involvement of epigenetics factors, while more endocrine systems get involved directly or indirectly and more communication systems such as the nerve system and the immune system. While dozens of proteins and many systems might be involved, an adverse effect could be visible in test animals (and possibly other adverse effects not noticed due to the insensitive test protocols, wrong doses or lacking endpoints). Far from being a linear system from exposure to effect with only one mode of action-as the 'human relevance'-tool assumes- this multitude of reactions cannot be assessed by scientists or regulators for a single chemical with reasonable certainty.

Science disregarded in favour of assumptions and unproven theories.
Using small differences observed between humans and the test animals (there will always be small differences), industry smartly started proposing and assuming that these differences are relevant and could be used to disqualify an observed effect. Based on old US-ideas, industry lobby club ILSI and Syngenta (Meek, 2003)[3]

3 A Framework for Human Relevance Analysis of Information on Carcinogenic Modes of Action, M. E. (Bette) Meek, John R. Bucher, Samuel M. Cohen, Vicki Dellarco, Richard N. Hill, Lois D. Lehman-McKeeman, David G. Longfellow, Timothy Pastoor, Jennifer Seed, and Dorothy E. Patton, Critical Reviews in Toxicology, 33(6):591–653, 2003

developed the 'human relevance' tool. Meek is an industry consultant covered as a Canadian academic scientist and active for ILSI for a big part of her career. In the next step industry linked people such as Bette Meek, Alan Boobis (claims to be a UK university professor but in reality works for industry (ILSI) for his entire career, even served many years as chair of board of trustees) and Josef Schlatter (worked for cigarette industry for a long time and more than 15 years for ILSI) and managed to 'copy & paste' the ILSI-approach into a IPCS/WHO framework on human relevance[4]. This is clearly serving industry agenda and not protecting citizens. It is sad to note that civil servants of involved countries didn't stop this industry campaign or ignorantly supported it.

Curiously, a peer-review study on the IPCS/WHO-framework[5] shows that the 'human relevance' tool is far from operational and would lead to subjective outcome and missing multiple mode-of-actions, missing vulnerable phases of life and ranges of susceptibility. It is unlikely that the tool will be operational in the foreseeable future with a solid scientific basis.

Let me demonstrate with a famous example what can happen if you would allow the 'human relevance' tool to be used for endocrines. About 40 years ago, top-level cancer test laboratories discovered that benzene is a multi-potent carcinogen[6] in rats. The target gland in rat is the Zymbal gland, an organ not present in humans. The outcome of the tests was heavily disputed by industry with exactly the same arguments, human relevance. The discussion caused much delay in protecting people but now finally there is a general agreement that benzene is a carcinogen. This example shows 'human relevance' will lead to delay in protecting people and potentially massive harm done.

It is not only the 'human relevance' tool we are worried about, but also for the connected topic of 'mode-of-action' we could easily tell a similar story as well as for the 'secondary effects' tool. These tools are mainly speculation based on unproven theories, assumptions and reasoning's, serving only one purpose and that is reducing costs for industry and ensuring unlimited access of chemicals to the market. We ask you not to support any of these 'tools' for the final criteria that will be proposed by Commission and to eliminate them from the discussions in future Commission inter-services consultation.

EFSA tries to re-write democratic adopted law.

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[4] IPCS Framework for Analyzing the Relevance, of a Cancer Mode of Action for Humans, Alan R. Boobis, Samuel M. Cohen, Vicki Dellarco, Douglas McGregor, M. E. (Bette) Meek, Carolyn Vickers, Deborah Willcocks, William Farland, Critical Reviews in Toxicology, 36:781–792, 2006.

[5] Journal of Toxicology and Environmental Health, Part B: Critical Reviews Mode of Action Frameworks: A Critical Analysis Kathryn Z. Guyton , Stanley Barone Jr. , Rebecca C. Brown, Susan Y. Euling, Jennifer Jinot & Susan Makris.

[6] Cesare Maltoni, Adriano Ciliberti, Giuliano Cotti, Barbara Conti, and Fiorella Belpoggi, Benzene, an Experimental Multipotential Carcinogen: Results of the Long-Term Bioassays Performed at the Bologna Institute of Oncology, Environmental Health Perspectives, Vol. 82, pp. 109-124, 1989

We also like to draw your attention to a few elements which in our view should have no place in the opinion at all. The EFSA scientific committee several times states that they prefer traditional risk assessment over a hazard approach. We feel EFSA has no say on this and should respect adopted democratic laws. We hope you will make clear to EFSA that this type of destructive remarks can have no place in an opinion and undermines the credibility of European law-making. These remarks could also be the unwanted result of the decision to include national civil servants in the EFSA working group preparing the opinion, who campaigned against the hazard approach in pesticide legislation from the start.

EFSA 'forgets' about the unborn.

Another bad point is the mentioning of 'modulation' in the opinion (section 3.1), an alleged reversibility of effects seen in test animals. While this is again a matter of speculation, only serving industry's agenda, the crucial concern of exposure of developing life (reversibility very unlikely) is disregarded by this type of statements. We hope you pay no attention to this flawed assumptions which are not resonated by serious scientists such as the Endocrine Society.

More unscientific industry inventions get a place in the opinion of EFSA.

Finally we are surprised to see the text on thresholds: "Thresholds of exposure are generally assumed below which there are no biologically significant effects". Again the topic of thresholds or no thresholds is just a matter of assumption. There are no serious data showing thresholds, let alone thresholds for endocrine active substances. The reference given by EFSA[7] makes it very clear why this strange assumption is included. The source is –again- an opinion of industry lobby club ILSI (Dybing, Kleiner, Schlatter, and Syngenta) published as a scientific article. We feel it is downgrading EFSA as an independent scientific body if the Scientific Committee keeps on including industry opinions as genuine 'science' in their opinions. It also shows EFSA has still a long way to go to exclude all industry-affiliated people in their panels and staff. We therefore urge you to speed up the policy on independence and conflict of interest of EFSA, making sure a road is chosen to a real independent and scientific way of making opinions, getting rid of all industry-affiliations in European agencies.

Conclusion

We hope you will take a strong position in the inter-services consultations on the criteria and defend the pesticide and biocide Regulation just as it has been adopted in co-decision:

- Make pesticides/biocides with 'endocrine disrupting properties' the regulatory category and,
- Deny every attempt to include loopholes for banning a pesticide such as 'human relevance' and 'secondary effect' serving commercial interest,

and take a strong stance on protecting European citizens.

[7] Dybing E, Doe J, Groten J, Kleiner J, O'Brien J, Renwick AG, Schlatter J, Steinberg P, Tritscher A, Walker R and Younes M, 2002. Hazard characterisation of chemicals in food and diet. dose response, mechanisms and extrapolation issues. Food and Chemical Toxicology, 40, 237-282.

Furthermore we ask you to,

- Consider all pesticides which are known for academic studies to be a chemical with endocrine disrupting properties (review of McKinlay[8] could be used as a basis) as those who should be banned in principle (positive list) while they can only be removed from the positive list if industry shows in in-vivo tests (covering all life phases, and adequate endocrine endpoints) within a fixed timescale (end 2014) that there are no adverse effects observable;
- Include by end 2013 mandatory screening tests for all endocrine system in the pesticide data requirements with a deadline for delivering outcome at the end of 2014; all pesticides showing positive results in the screening test should be put on the 'positive list' of to be banned pesticides in principle and they can only be removed if industry shows within a narrow timeframe on the basis of an adequate in-vivo test that no adverse effects will be observed;
- Any pesticide from the 'positive list' monitored in body fluid, water, air, soil, etc. should lead to an immediate ban of the pesticide, not awaiting further testing and evaluation.

Looking forward to your reaction,

Sincerely yours

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PAN Europe

cc. Mr. Potocnik, DG Environment
Mrs. Geoghegan-Quinn, DG Research

8 R. McKinlay, J.A. Plant, J.N.B. Bell, N. Voulvoulis, Endocrine disrupting pesticides: Implications for risk assessment, Environment International 34 (2008) 168–183