A POISONOUS INJECTION

HOW INDUSTRY TRIES TO WATER DOWN THE RISK ASSESSMENT OF PESTICIDE MIXTURES IN EVERYDAY FOOD

SUMMARY

This PAN Europe report reveals a well planned and orchestrated attempt of industry to undermine policies meant to evaluate the toxicity of chemicals mixtures (cumulative risk assessment, CRA). This is done by putting industry-linked experts in crucial positions in expert panels of the World Health Organisation (WHO) and of the European Food Safety Authority EFSA. A massive delay in policy implementation is the result. Eight years after the EU mandated such risk assessments for pesticide residues in food, EFSA still fails to carry them out, leaving consumers and citizens unprotected against the harms of mixtures of pesticides in food.

Every day people are exposed to dozens of pesticide residues in food, in fruit and vegetables, and to hundreds of other chemicals during their lifetime. Food standards however are based on a single exposure, which is unrealistic. Consequently these standards do not protect humans against the potential health damage of mixtures especially over an extended period of time. When politicians finally agreed to change the food standards, industry developed their views on CRA and set out to infiltrate government bodies that would implement the policy on CRA.

The WHO was an easy target for industry because industry-linked scientists -who kept their bias hidden- could simply outnumber the other attendants in the WHO-panel and impose the industry position on the WHO. Our research shows that out of the WHO-planning group on CRA, 73% of the members were not impartial observers, but rather had industry-links and conflicts of interest, while 5 out of the 6 authors that published the final WHO-framework had strong industry-ties. A handful of industry-linked people therefore managed to dominate the WHO. Remarkably, none of them was an active scientist nor were any involved in developing research.

With regard to the European Food Safety Authority EFSA, industry has taken a similar approach: infiltration by industry-linked experts in EFSA panels and working groups. Of the experts having worked on CRA for EFSA, PAN Europe observed that 19% had a formal relation with industry lobby group ILSI (International Life Sciences Institute) and that even the majority (52%) had a connection with industry. The same people dominating WHO managed to dominated EFSA on CRA, where they have been found 'fertile ground'. Many national experts and civil servants present in EFSA panels have been in their positions their entire career and were reluctant to change their mindset. Many felt that cumulative mixture toxicity is a non-issue. Therefore, EFSA's work on CRA in the first 6 years has tended to lean towards a position that would qualify mixture toxicity as largely irrelevant and that no extra consumer protection is necessary. Only after an intervention by Health DG SANCO in 2011, was EFSA forced to change course and take CRA seriously. Still the EFSA pesticide panel refused to cooperate and in 2012 EFSA terminated the mandate of the panel because of the "lack of significant progress"[1]. At the same time, the European Parliament forced EFSA to adopt a conflict of interest policy, leading to a partial reduction in the membership of infiltrators. The outcomes of these measures remains to be seen, but this is the first example of the Commission rolling back a clear example of industry infiltration. Again, as in the case of the WHO, only a few members of the EFSA panels (22%) were scientists actively carrying out research. An incredibly small number for an institute that claims to base their opinions on science.

Still industry hasn't given up and continues to try to create credibility for another industry-promoted CRA-tool (probabilistic risk assessment, PRA) by joining forces in the EU funded research program Acropolis. The same industry-linked people that were active in WHO and in EFSA now gather in this program, co-managed by food industry group Freshfel. They promote and defend this tool (PRA) to allow a certain level of health damage to people in an attempt to 'neutralise' the coming policy on CRA, which they were unable to stop. The tool is to "prove that pesticide use is safe[2]" according to coordinator Van Klaveren. Acropolis also shows many dual roles, people simultaneously active in

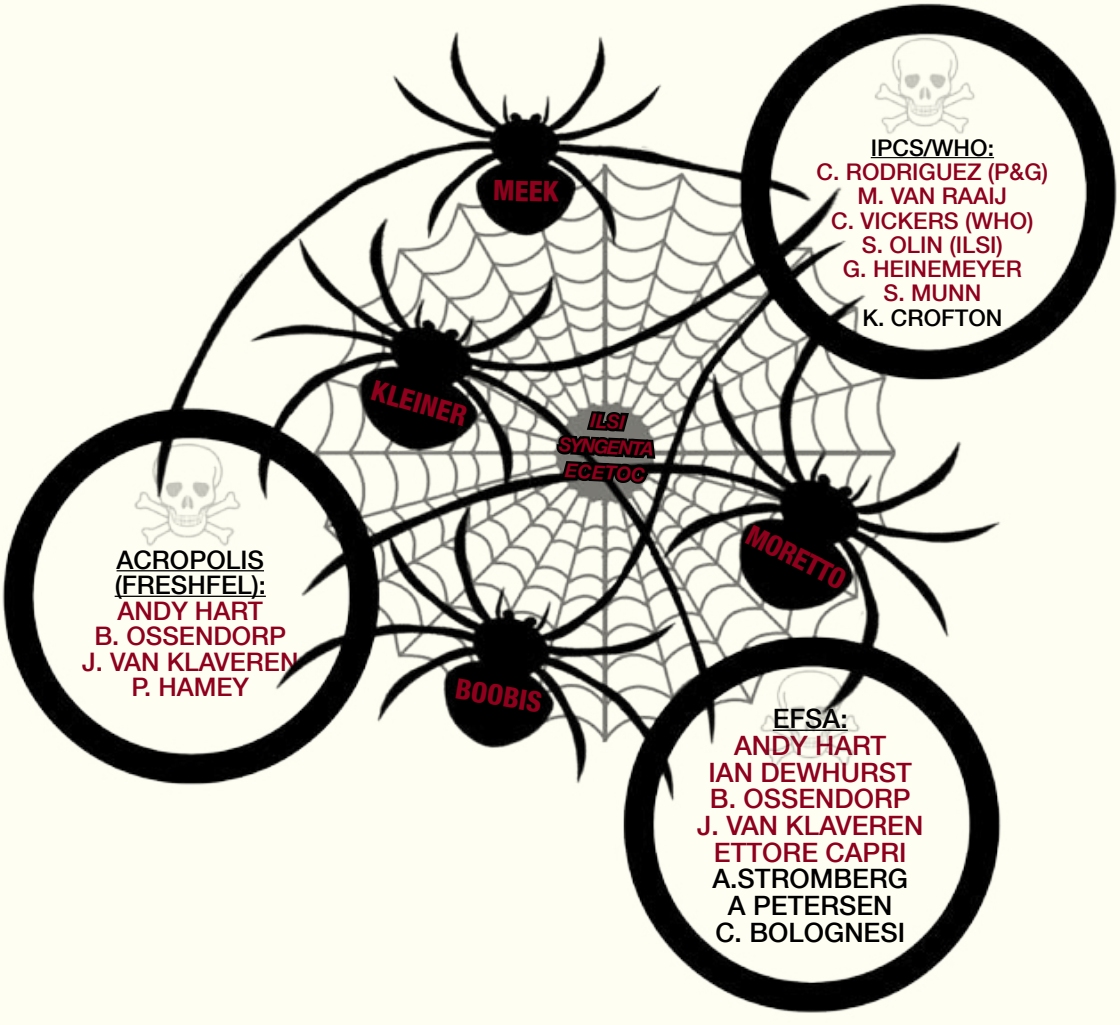
1. Minutes from an EFSA/Commission teleconference of 11 July 2012, see www.pan-europe.info/Campaigns/pesticides/cum_syn_effects.html under "useful information".

2. www.acropolis-eu.com/object_binary/o4422_ACROPOLIS_03.pdf

developing, advising and implementing tools. The current EFSA science director Juliane Kleiner is a clear example of having dual roles.

PAN Europe calls for the WHO to revise her procedures and adopt a proper conflict of interest policy to prevent a situation –such as on CRA- were industry completely dominates policy making. Also the continuing close cooperation of WHO with industry and ILSI should be ended. The EFSA should be more aware of infiltration activities. This should be done by strengthening the policy on conflict of interest and taking the full career of experts and the potential industry-links and bias in their work into consideration. Independent and active scientists should be the majority of the experts in EFSA panels and not a minority (22%) as in the case of CRA.

A POISONOUS INJECTION BY A NETWORK OF INDUSTRY-LINKED EXPERTS (SPIDERS) AND ALLIES (RED) IN EXPERT PANELS; NEUTRAL EXPERTS IN BLACK



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1.

INTRODUCTION

The assessment of the safety of use of pesticides is based on exposure of humans and the environment to single substances. This does not reflect reality since laboratory analysis of the national authorities in every European country has clearly shown that people are exposed to dozens of pesticides at the same time every day[3] and hundreds of other chemicals during lifetime[4]. While there is a scientific consensus that the single-substance approach is flawed, it took decades before a political decision was made to change the system and chances are it will years more for an effective implementation of the policy. The reluctance for change came from all sides. For regulators, it is hard to admit that the approach they have taken their entire career is flawed; for politicians it is hard to admit that their continuous claims that "our food is safe" were not entirely true; while industry is concerned about extra costs and potential bans on pesticides.

In the US, politicians were the first to force the needed change by including a cumulative assessment[5] in the FQPA (Food Quality Protection Act) of 1996. In Europe, cumulative assessment was included for the first time in the pesticide Residue Directive 396/2005[6] and later in other legislation. This assessment however will only be operational when the European Food Authority (EFSA) develops the methods for this assessment. Again the same reluctance can be seen among EFSA staff and panels and now -eight years later- cumulative assessment is still not operational. EFSA therefore fails to protect people and accepts potential health damage of the European population.

Our research questions are: What has caused this massive delay? And what role has industry and other actors played in the way EFSA developed cumulative assessment? We approach these questions by looking at EFSA panels, European research programmes, and at the work of international risk assessment bodies.

3. European Food Safety Authority; The 2010 European Union Report on Pesticide Residues in Food. EFSA Journal 2013;11(3):3130. [808 pp.] doi:10.2903/j.efsa.2013.3130, www.efsa.europa.eu/efsajournal

4. See for instance: WWF-UK National Biomonitoring Survey 2003, CONTAMiNATION

5. A cumulative assessment refers to an assessment of adverse effects of multiple pesticides/chemicals on the body which might cause an increased/higher effect –additive/synergistic- than the effect of exposure to a single chemical

6. REGULATION (EC) NO 396/2005 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC, art. 14.2.b.

2.

METHODS USED FOR THE ANALYSIS OF POTENTIAL CONFLICTS OF INTEREST AND OF THE SCIENTIFIC EXPERIENCE OF EXPERTS

PAN Europe has analysed if the people contributing to cumulative risk assessment (CRA) had any conflict of interest[7], now or in the past and if the experts are active scientist. Our analysis was focused on:

- Articles in scientific journals by searching PubMed and Science Direct, using the names of the contributors as search terms. We looked at the content of their articles and checked what other authors and co-authors were involved, if there were links to ILSI or industry, and if these articles favoured industry's point of view. We also looked at the publications of each member in the last five years to find out if they were actively publishing scientists[8] and therefore aware of recent developments in science (the detailed outcome of the analysis can be found in Annex I).

- EFSA's declarations of interest (DoI) and online research for connections with industry activities (ILSI, ECETOC, SETAC) or other ties with industry (an analysis of the reported conflicts of interests can be found in Annex II).

- Access to documents requests (ATD) concerning all communication, documents, meetings, deliverables, declarations of interests (DoI) of EFSA/EU and organisations/ persons involved in EU funded programs and the EFSA pesticide panel (PPR) external reports. It must be noted that EFSA severely hampered our research by denying access to most of the relevant information needed to critically assess the decision-making processes.

- Finally, we looked if these people promoted certain (industry) tools and asked for research funding to develop it further and - at the same time- being active in the research work they asked for in the first place (for example, the Acropolis program, an industry-promoted CRA-tool). In essence, their potential dual roles.

7 .PAN Europe uses the OECD definition of a conflict of interest: A "conflict of interest" involves a conflict between the public duty and private interests of a public official, in which the public official has private-capacity interests which could improperly influence the performance of their official duties and responsibilities.

8. PAN Europe uses as a definition for an actively publishing scientist, someone who on average publishes at least 1 original article per year in the last 5 years in international peer-reviewed journals. Comments, opinions and reviews do not count.

3.

EVALUATION OF THE REGULATORY ATTEMPTS TO IMPLEMENT CUMULATIVE RISK ASSESSMENT

(BASED ON THE TECHNICAL ANALYSIS IN ANNEX III).

Alarmed by the initiative of US regulators in 1996 to include cumulative assessment in risk assessment of chemicals[9], industry started thinking about their answer. Industry lobby group ILSI (International Life Sciences Institute, an institute financed by agro-food and chemical companies designed to deliver 'scientific' proposals for regulators) for instance, in 1998 initially positioned[10] themselves in order to minimise the business consequences of the outcome of a cumulative risk assessment. Cumulative risk assessment in their proposals should only be considered if it is about chemicals with a common mechanism of action, and this was so strictly defined (common target, common toxic intermediate, same critical effect, etc.) that it is hard to imagine two chemicals would be qualified as being in the same group for cumulative assessment. There will be always tiny differences in the outcome of pesticide testing on animals which can be used to suggest that a target, an intermediate or effect is different.

Several ILSI-linked people (with a university- or civil servant-position) then set out to be a member of government bodies expected to take a position on cumulative risk assessment such as the World Health Organisation (WHO) and European Food Authority EFSA and sell their ideas.

The lack of resources of other experts and scientists might have given these industry-linked people an advantage when they 'volunteered' to work on cumulative risk assessment. It is also the culture of regulators that gives industry an advantage. Moretto, an Italian professor and one linked to ILSI[11], probably best expressed the prevailing culture by saying that exposure generally happens at low doses and he believes they pose no harm[12]. Larsen, a Danish civil servant at the national Food Institute, and other industry-affiliated people[13] take the same view saying that cumulative effects are less of a concern at

9. Amendment to the FQPA, the Food Quality Protection Act.

10. ILSI (1998) Aggregate exposure assessment. Washington, DC, International Life Sciences Institute Research Foundation, Risk Science Institute, 215 pp.

11. Co-chair of the sub-team on Assessment of cumulative exposure to chemicals of ILSI/HESI project RISK 21 (Declaration of interest, EFSA, 2011)

12. Angelo Moretto, Exposure to multiple chemicals: when and how to assess the risk from pesticide residues in food, Trends in Food Science & Technology 19 (2008) S56eS63

13. Larsen was part of ILSI's: Scientific Advisory Committee Advises on ILSI Europe's Scientific Working Programme and participated and chaired ILSI meetings (.PAN report on TTC)

relatively low exposure levels compared to high exposure levels since they are primarily caused by various thresholds and saturation phenomena.[14] This is the typical industry view, saying that below a certain assumed threshold there is no effect, and if there would be an effect, it could be reversible given the hypothetical feedback mechanism in the body. Not much science underlies these assumptions. Thresholds are almost impossible to prove. And regarding reversibility they conveniently ignore that the developing organisms lack such feedback mechanisms. The industry approach would lead to a cosmetic operation, meaning that cumulative risk assessment is hardly applied.

Apart from the industry discussion on the narrow definition of cumulative exposure, with which PAN Europe disagrees, there is much more on cumulative risk assessment than the discussion on chemicals with exactly the same mechanism of action (a tiny fraction of all mixtures). If two chemicals have the same effect (but not the same mechanism-of-action, MOA), it is very unlikely this would not lead to any increased cumulative effect. Additionally, some chemicals are known to give synergistic effects (stimulate each other) and there is no evidence that justifies simply ignoring this phenomenon. Even more importantly, humans are exposed not only to pesticides but also numerous other chemicals, which may contribute to cumulative effects. And finally without a similar MOA and without a similar effect, wouldn't there be any cumulative effect at all since the body is interconnected through three main communication systems (nerve, immune, endocrine) and shouldn't the whole issue be looked at from a more holistic point of view? Industry has tried to keep all these questions under the table and managed to get their way for many years.

A WHO/IPCS 2007-workshop on 'the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals' was dominated very much by industry representatives and industry-proxy's, while almost no independent scientists were present, and no-one from health NGO's[15]. The ILSI-position got a prominent place in the workshop report and the ILSI-position in subsequent 'scientific' articles was even upgraded to a WHO/IPCS 'framework'[16]. A policy seems to be absent at the WHO to prevent imbalance and industry-domination in WHO workshops.

14. Trine Klein Reffstrup, John Christian Larsen, Otto Meyer, Risk assessment of mixtures of pesticides. Current approaches and future strategies, Regulatory Toxicology and Pharmacology 56 (2010) 174–192

15. ASSESSMENT OF COMBINED EXPOSURES TO MULTIPLE CHEMICALS: REPORT OF A WHO/IPCS INTERNATIONAL WORKSHOP ON AGGREGATE/ CUMULATIVE RISK ASSESSMENT, WHO, 2009

16. M.E. (Bette) Meek, Alan R. Boobis, Kevin M. Crofton, Gerhard Heinemeyer, Marcel Van Raaij, Carolyn Vickers, Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework, Regulatory Toxicology and Pharmacology 60 (2011) S1–S14

The EFSA was the next battleground and from 2006 up to 2011 industry-proxy's helped to lead the EFSA to limit itself to an ILSI definition of risk assessment. It is known that many experts in the EFSA panels (especially civil servants from national institutes) are of the opinion that cumulative exposure is a 'non-issue' while they also feel that the opinions of industry are generally credible[17]. Even the current chair of the EFSA PPR-panel believes that the system they developed over the years with uncertainty factors for the ADI is so "overprotective" that cumulative risk assessment will pose no risks[18]. The many industry-affiliated people in panels and EFSA-meetings therefore found 'fertile soil' to feed their ideas in the EFSA opinions.

The 2008-EFSA opinion on CRA was used as a basis for an article[19] published by panel members Boobis, Ossendorp, Hamey and Moretto and gives a good look into the 'culture' in the EFSA panel. They conclude that "*The available data suggest that the risk from combined exposures to residues of pesticides with different modes of action is not appreciably greater than the risk from residues of the individual pesticides, when exposure is below the respective ADIs or ARfDs. In this situation, the overall risk is determined by the compound that poses the greatest risk (e.g. the highest HQ). Hence, there is no need to assess combined exposure to those pesticides with different modes of action and different target tissues, occurring as residues in foods*". Except from a few limited cases, they conclude that the food standards are safe.

This only changed after intervention of DG SANCO in 2011[20] forcing EFSA to at least include similar responses (same adverse effects) in the cumulative assessment, also thanks to the work of Prof. Andreas Kortenkamp and DG Environment initiatives[21].

The EFSA pesticide PPR panel however apparently kept on resisting against the change and finally EFSA management terminated the mandate of the PPR panel[22] ("*EFSA management has high concerns about the lack of significant progress of the PPR panel*") and moved the work to EFSA staff.

17. The current chair of EFSA PPR-panel Bernadette Ossendorp published with ILSI-chair of trustees Prof. Boobis on cumulative (Alan R. Boobis, Bernadette C. Ossendorp, Ursula Banasiak, Paul Y. Hamey, Istvan Sebestyen, Angelo Moretto, Cumulative risk assessment of pesticide residues in food, Toxicology Letters 180 (2008) 137–150) and is active in the research program ACROPOLIS of food industry. Other civil servants such as UK civil servants Andy Hart, Ian Dewhurst and Diane Bedford play a similar role.

18. The current chair of the EFSA PPR-panel, Ms. Ossendorp, a Dutch civil servant, explained that the system is already 'over conservative' and the issue of cumulative risk assessment of a minor nature. They (EFSA) are forced to work on this topic for political reasons while they know already the exposure to pesticide residues is safe. She also pointed out that they see it as their job to 'educate' people and explain them about their unfounded fears of chemicals. People are generally exposed at low doses which will not lead to any damage. The discussion on diseases is a 'hype', according to Ms. Ossendorp; diseases are not rising. (personal communication, 16-11-10).

19. Alan R. Boobis, Bernadette C. Ossendorp, Ursula Banasiak, Paul Y. Hamey, Istvan Sebestyen, Angelo Moretto, Cumulative risk assessment of pesticide residues in food, Toxicology Letters 180 (2008) 137–150.

20. SANCO letter to EFSA, 26-09-2011, www.pan-europe.info/Campaigns/pesticides/cum_syn_effects.html under "useful information".

21. Prof. Dr. Andreas Kortenkamp, Assoc.-Prof. Dr. Thomas Backhaus, Dr. Michael Faust, State of the Art Report on Mixture Toxicity, 2009, EU Commission report 070307/2007/485103/ETU/D.1

22. Minutes from an EFSA/Commission teleconference of 11 July 2012, see , www.pan-europe.info/Campaigns/pesticides/cum_syn_effects.html under "useful information".

Still the final outcome at EFSA is not clear.

We also explored if industry has infiltrated EFSA and EU Commission research programmes to push their agenda from that side. This part will be dealt with in the last chapter.

The SANCO scientific committees are still close to the industry position except the inclusion of a requirement to assess 'known mixtures' by dose-addition (additively counting the doses people are exposed to, if known), also in case of dissimilar MOA[23].

In conclusion, much of the delay is caused by focussing on a narrow definition of CRA, as a likely result of industry infiltration, but also because of the reluctance of many regulators to change the system. This shows that regulators have the power to stop democratic decisions and that they don't hesitate to use this power. The WHO and EFSA are both heavily stacked with industry-linked experts (see for details the next chapters) and these institutes appear to lack proper checks and balances to arrive at fair and scientific outcomes.

PAN Europe feels the current risk assessment of pesticides is far from conservative. The safety factors used are not sufficient in all cases (confirmed by a recent study of Martin[24]). Martin et al. qualify the statements of regulators on 'over conservative' even a 'myth'. Apart from not taking cumulative effects into account, many other negative influences (such as the hundreds of other chemicals people are exposed to as well as other stress factors) are not accounted for. PAN Europe therefore calls for a cumulative approach on similar effects and -on top of this- to account for other chemicals and stress factors, to include an extra safety factor of 10 in risk assessment[25]. The idea to introduce probabilistic modelling should be abandoned since this again would introduce extra danger (a part of the population will not be protected)[26].

23. Scientific Committee on Health and Environmental Risks, Scientific Committee on Emerging and Newly Identified Health Risks, and the Scientific Committee on Consumer Safety, Toxicity and Assessment of Chemical Mixtures, DG SANCO, November/December 2011.

24. Olwenn V Martin, Scholze Martin and Andreas Kortenkamp, Dispelling urban myths about default uncertainty factors in chemical risk assessment – sufficient protection against mixture effects?, Environmental Health 2013, 12:53

25. PAN Europe 2011 position paper on our website, www.pan-europe.info/Campaigns/pesticides/cum_syn_effects.html under "useful information".

26. PAN Europe 2013 letter to Commissioner Borg on probabilistic modelling on our website, www.pan-europe.info/Campaigns/pesticides/cum_syn_effects.html under "useful information".

4.

INTERNATIONAL DEVELOPMENTS, THE WORK OF THE WHO AND THE OECD ON CRA

The World Health Organization (WHO) has focused her attention on cumulative risk assessment for several years through meetings and workshops. One of the first meetings, the WHO/IPCS meeting on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals, was convened in October 2004 in Cincinnati, USA. The meeting was also attended by industry lobby group the "International Life Sciences Institute", ILSI (Steve Olin) and the European industry lobby group "European centre for Ecotoxicology and Toxicology of Chemicals", ECETOC (Michael Gribble) as well as industry consultant Bette Meek. The WHO concluded that a workshop should be convened on "Aggregate/cumulative Risk Assessment", to produce a report including an internationally-agreed framework, and declared this as a new "top priority activity".[27] Remarkably, current EFSA-science director Juliane Kleiner attended the WHO/IPCS meeting right after she stopped her seven year career working for ILSI. Kleiner highlighted industry proposals on pesticides (genotox, risk-benefit)[28].

In March 2007 Kleiner, Meek and Boobis where the members of the planning group[29] for the WHO/IPCS workshop on Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals in Washington, USA. The WHO planning group was dominated by industry and industry-linked people (73% was industry-linked; *see Table 1*). Other participants

27. www.who.int/ipcs/methods/harmonization/organization/final_report.pdf

28. The notes say: EFSA (Dr Juliane Kleiner) highlighted work on: assessment of genotoxic and carcinogenic substances (information exchange with WHO and ILSI is taking place); transparency in risk assessment; and uncertainty in exposure assessment (cooperation is in place with IPCS). She also mentioned proposals to work on aggregate/cumulative risk assessment and a paradigm for risk benefit analysis.

29. Members of the Workshop Planning Group were: Bette Meek (workshop Chair), Alan Boobis, Kevin Crofton, Gerhard Heinemeyer, Sumol Pavitrannon, Carlos Rodriguez, Marcel Van Raaij, Nena Waight-Sharma, European Chemicals Bureau (Sharon Munn), European Food Safety Authority (Juliane Kleiner) and International Life Sciences Institute (Stephen Olin).

included additional industry and industry-linked people such as Ian Dewhurst (UK), Angelo Morretto (Italy), John Christian Larsen (Denmark), and Josef Schlatter (Switzerland)[30]. A total of 26 people, dominated by industry, therefore decided on the position of IPCS/WHO.

Kleiner and Meek, and again ILSI (Stephen Olin) and ECETOC (John Doe, Syngenta), were also present at the meeting of the WHO/IPCS Steering Committee on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals in Berlin in May 2007.[31] As a liaison, Bette Meek discussed the progress on aggregate/cumulative risk assessment, on which the Committee supported the next phase in developing the framework, while ECETOC and ILSI offered to assist by the developing case studies. The close cooperation between WHO and ILSI/ECETOC continues and apparently no one questions any conflict of interest.

Meek and Boobis finally took advantage of their IPCS/WHO-involvement and published an opinion in a scientific journal based on this workshop[32], including the IPCS/WHO framework for cumulative assessment. The article puts forward many elements of the industry proposal for risk assessment with a very high burden of proof for regulators to show similar action of chemicals. Additionally, the article promotes a series of 'higher–tier' risk assessment options to escape from any occurring cumulative risk problem and promote the so-called 'probabilistic risk assessment', a tool which allows for a certain level of harm to be done to people. Five of the six authors of the final IPCS/WHO-framework *(Table 1)* had industry interests, a clear conflict of interest given the purpose of the work.

None of the people at the WHO planning group was an active scientist *(Table 1 and Annex I)*, many have never worked on any original research or published in scientific journals. It is therefore very unlikely recent scientific insights have been included. This makes the scientific quality of the work at WHO highly questionable.

30. /www.who.int/ipcs/methods/harmonization/areas/aggregate/en/

31. www.who.int/ipcs/methods/harmonization/hsceight_report.pdf

32. M.E. (Bette) Meek, Alan R. Boobis, Kevin M. Crofton, Gerhard Heinemeyer, Marcel Van Raaij, Carolyn Vickers, Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework, Regulatory Toxicology and Pharmacology 60 (2011) S1–S14.

TABLE 1. SUMMARY OUTCOME OF THE PAN EUROPE ANALYSIS OF THE WORK OF WHO (ANNEX I PROVIDES FOR A MORE DETAILED ANALYSIS OF THE SCIENTIFIC WORK OF PEOPLE, WHILE ANNEX II FOCUSES ON OTHER EVIDENCE SUCH AS DECLARATIONS OF INTERESTS AND PUBLIC INFORMATION)

	WHO planning group on CRA	Author publication WHO framework[33]	Known links with ILSI or other industry lobby groups	Known links with specific private companies	Active scientist
Bette Meek	Yes	Yes	Yes, many consultancies for ILSI	Yes, many consultancies for chemical industry	No
Alan Boobis	Yes	Yes	Yes, chair of Board of trustees, member Board ILSI	Yes, many consultancies for chemical industry	No
Kevin Crofton	Yes	Yes	No	No	No
Gerhard Heinemeyer	Yes	Yes	No	Yes, with Procter & Gamble, defending TTC	No
Sumol Pavitrannon	Yes	No	No	No	No
Carlos Rodriquez	Yes	No	Yes, industry employee, representing CEFIC and ECETOC	Yes	No
Marcel van Raaij	Yes	Yes	Yes	Yes	No
Carolyn Vickers	No	Yes	Yes, while being at the WHO secretariat, she apparently defends ILSI-proposals	Yes	No
Sharon Munn	Yes	No	Yes, on several ILSI-tools	No	No
Stephen Olin	Yes	No	Yes, he is ILSI employee	Yes	No
Juliane Kleiner	Yes	No	Yes, worked for ILSI and kept cooperating with them being at EFSA[34]	Yes	No
Josef Schlatter	No	No	Yes, many years connected to ILSI	Yes	No
Ian Dewhurst	No	No	Yes	Yes	No
Angelo Moretto	No	No	Yes, many years formal connections	Yes	No
Nena Waight-Sharma	Yes	No	No	No	No
John Christian Larsen	No	No	Yes, many years connected to ILSI	No	No

33. M.E. (Bette) Meek, Alan R. Boobis, Kevin M. Crofton, Gerhard Heinemeyer, Marcel Van Raaij, Carolyn Vickers, Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework, Regulatory Toxicology and Pharmacology 60 (2011) S1–S14.

34. www.pan-europe.info/News/PR/130910.html

The close cooperation between the WHO and industry groups such as ILSI continues. In February 2011, another joint WHO-OECD-ILSI meeting was organised: an International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals, this time in Paris.[35] Again Boobis and Meek, and now also Moretto, were present, as well as ILSI, ECETOC and other industry representatives such as Carlos Rodriquez from industry lobby group CEFIC.[36] Though independent experts were also present (especially from Denmark), the meeting was dominated by industry representatives and industry-linked people like Rodriquez, Meek, Boobis, Van Raaij, and Moretto. The outcome was not very clear since different cases studies were discussed, but the use of TTC (Threshold of Toxicological Concern) another industry sponsored risk assessment approach[37] similar to probabilistic risk assessment by allowing a level of harm, received multiple recommendations.

35. www.oecd.org/env/ehs/testing/workshopreportonwhooecdilsihesiiinternationalworkshoponriskassessmentofcombinedexposurestomultiplechemicals.htm

36. ILSI: Dr Stephen Olin, Michelle Embry; ECETOC: Carlos Rodriguez (Proctor & Gamble), Neil Carmichael; Elizabeth Shipp; Susan Felter (HESI, Procter & Gamble), Gary Mihlan (Bayer CropScience), Rosemary Zaleski (ExxonMobil Biomedical Sciences).

37. See PAN report on TTC

Before and after the OECD ILSE/HESI workshop, industry also held two workshops on the subject of risk assessment and combined exposure. The ILSI/RISK21 Workshop Realizing the Future of Risk Assessment was held January 11th 2011 in Washington[38] and the ECETOC Workshop on Combined Exposure to Chemicals was held on June 11-12th 2011.[39] Both these workshops were attended by many industry-linked people including Boobis, Meek and Moretto.

38. www.hesiglobal.org/i4a/pages/Index.cfm?pageID=3546, www.hesiglobal.org/files/public/Committees/Risk21/Jan_2011_Workshop/Risk21ParticipantsJan2011.pdf

39. www.ecetoc.org/index.php?mact=MCSoap,cntnt01,details,0&cntnt01by_category=22&cntnt01order_by=date%20Desc&cntnt01template=display_list_v2&cntnt01display_template=display_details_v2&cntnt01document_id=5034&cntnt01returnid=59

In conclusion, a massive attempt has been made on the international level to impose the industry view of cumulative risk assessment to institutes such as WHO/IPCS and OECD. It is more than likely that this was a systematic effort managed (and probably paid) by industry to infiltrate international institutes and unfairly influence policy. Employees of industry lobby groups and industry-linked experts had a dominating role.

5.

THE EUROPEAN CUMULATIVE RISK ASSESSMENT AT FOOD AUTHORITY EFSA.

During the eight years EFSA has worked on this topic, 27 different people contributed significantly to cumulative risk assessment (*Table 2*). Together, they were active in three different working groups[40], wrote three opinions[41], one guidance document[42] and/or contributed to six external research reports[43]. A rough estimate indicates that more than a million Euros were spent on these activities[44].

Based on our analysis approach as described in the chapter 2, we assessed five elements of a potential conflicts of interest and scientific quality:

- Formal ILSI connections
- Connection to ILSI in publications
- Connections with industry (workshops, stocks, et cetera)
- Dual roles

Additionally we investigated whether a person is an actively publishing scientist because it is very important that panel members understand recent insights in science and take part in academic discussions.

40. PPR WG Cumulative Assessment Groups of Pesticides, PPR WG Probabilistic Methodology Mandate 2009 and PPR WG Relevance of Dissimilar Mode of Action for Cumulative Risk Assessment

41. EFSA Panel of the Panel on Plant Protection Products and their Residues (PPR Panel)/Opinion of the Scientific Panel on Plant Protection products and their Residues to evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005. EFSA Journal (2008) 704, 1-85; EFSA Panel on Plant Protection Products and their Residues (PPR). Scientific Opinion on Risk Assessment for a Selected Group of Pesticides from the Triazole Group to Test Possible Methodologies to Assess Cumulative Effects from Exposure through Food from these Pesticides on Human Health. EFSA Journal 2009; 7 (9); 1167. [187 pp.]. doi:10.2903/j.efsa.2009.1167; EFSA Panel on Plant Protection Products and their Residues (PPR). Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile. EFSA Journal 2013;11(7):3293. [131 pp.]. doi:10.2903/j.efsa.2013.3293

42. EFSA Panel on Plant Protection Products and their Residues (PPR). Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues. EFSA Journal 2012;10(10):2839. [95 pp.]. doi:10.2903/j.efsa.2012.2839

43. FERA (2009). Cumulative Exposure Assessment of Triazole Pesticides; Klaveren et al (2010). Cumulative Exposure Assessment of Triazole Pesticides; DTU (2012). Identification of Cumulative Assessment Groups of Pesticides; Kortekamp et al (2012). Investigation of the state of the science on combined actions of chemicals in food through dissimilar modes of action and proposal for science-based approach for performing related cumulative risk assessment; Glass et al (2012). Collection of the state of the science on combined actions of chemicals in food through dissimilar modes of action and proposal for science-based approach for performing related cumulative risk assessment; RIA (2013). Toxicological data analysis to support grouping of pesticide active substances for cumulative risk assessment of effects on liver, on the nervous system and on reproduction and development

44. EFSA granted a total of €748.039,57 for five of the six external reports. EFSA gives no insight in the fees the 27 contributors have received.

TABLE 2.
Summary outcome of the PAN Europe analysis of the work of EFSA (Annex I provides for a more detailed analysis of the scientific work of people, while Annex II focuses on other evidence such as declarations of interests and public information).

Name	Profession	Position at EFSA	Formal ILSI connection	ILSI connection publications	Connection with industry	Actively publishing scientist	Dual roles	Also active in WHO on this topic
Alan Boobis	Professor and industry consultant	PPR member, workgroup member and contributor to opinion(s)	Yes	yes	yes	no	yes	yes
Alberto Mantovani	Professor	PPR member, workgroup member and contributor to opinion(s)	No	no	some	yes	no	no
Andreas Kortenkamp	Professor	Workgroup member and contributor to opinion(s) and an external report	No	no	no	yes	no	no
Andy/Andrew Hart	Civil servant	PPR member, workgroup member and contributor to opinion(s) and an external report	Yes	yes	yes	no	yes	no
Angelo Moretto	Professor	PPR member, workgroup member and contributor to opinion(s) and an external report	Yes	yes	yes	no	yes	yes
Anita Stromberg	Civil servant	PPR member and contributor to guidance document	No	no	no	no	no	no
Annette Petersen	Civil servant	PPR member and contributor to guidance document	No	no	no	no	no	no
Antonio F. Hernandez	Professor	PPR member, workgroup member and contributor to opinion(s)	No	no	some	yes	no	no
Arne Büchert	Civil servant	PPR member, workgroup member and contributor to opinion(s)	No	no	no	no	no	no
Bernadette Ossendorp	Civil servant	PPR member, workgroup member and contributor to opinion(s) and an external report	no	some	yes	no	yes	no

Name	Profession	Position at EFSA	Formal ILSI connection	ILSI connection publications	Connection with industry	Actively publishing scientist	Dual roles	Also active in WHO on this topic
Christiane Vleminckx	Civil servant	PPR member, workgroup member and contributor to opinion(s)	No	no	no	no	no	no
Claudia Bolognesi	Researcher	PPR member, workgroup member and contributor to opinion(s)	No	no	no	yes	no	no
David Miller	Civil servant	Workgroup member and contributor to opinion(s)	No	yes	yes	no	no	no
Ettore Capri	Professor and industry consultant	PPR member	No	no	yes	yes	no	no
Ian Dewhurst	Civil servant	Contributor to opinion(s)	Yes	yes	yes	no	no	no
Jacob Klaveren	Civil servant	Workgroup member and contributor to opinion(s) and an external report	No	yes	yes	no	yes	no
Juliane Kleiner	Civil servant	Chief scientific advisor	Yes	yes	yes	no	no	yes
Karen Ildico Hirsch	Civil servant	PPR member, workgroup member and contributor to opinion(s)	No	no	no	no	no	no
Kyriaki Machera	Civil servant / consultant	PPR member, workgroup member and contributor to an external report	No	no	yes	no	yes	no
Maria Tasheva	Civil servant, retired	PPR member, workgroup member and contributor to opinion(s)	No	no	no	no	no	no
Mark Montforts	Civil servant	PPR member and workgroup member	No	no	no	no	no	no
Markus Müller	Consultant	PPR member, workgroup member and contributor to opinion(s)	no	no	no	no	no	no
Paul Hamey	Civil servant	Workgroup member and contributor to opinion(s)	No	yes	some	no	yes	no
Roland Solecki	Civil servant	Workgroup member and contributor to opinion(s)	No	yes	yes	no	no	no
Susanne Hougaard/ Bennekou	Civil servant / consultant	PPR member, workgroup member and contributor to opinion(s)	No	no	no	no	no	no
Ursula Banasiak	Civil servant	Contributor to opinion(s)	No	no	no	no	no	no
Yolanda Pico	Professor	PPR member and contributor to guidance document	No	no	no	yes	no	no

The results of our analysis show that there is a massive conflict of interest in EFSA panels and working groups. Of the 27 people analysed,

- 5 (19%) had a formal connection with ILSI
- 10 (37%) published in scientific literature with co-authors who were connected to ILSI
- 14 (52%) have a connection with industry
- Only 6 (22%) are active researchers
- Finally 7 (26%) had a dual role by contributing to EFSA while promoting industries views on cumulative risk assessment through EFSA research and/or the EC funded Acropolis program.

The analysis also shows that there is an overlap with the people active in WHO/IPCS. The main industry advocates at the WHO, Boobis and Moretto, also managed to get seats in EFSA panels. This shows determined motivation on the part of these people regarding cumulative risk assessment since neither the EFSA nor the WHO pays their panellists for the hours spent at meetings, travelling and commenting.

MOST NOTABLE ACTORS

JACOB VAN KLAVEREN

Jacob van Klaveren is a civil servant for the National Institute for Public Health and the Environment (RIVM) in the Netherland. Until 2009, he was employed by the semi-commercial Institute of Food Safety (RIKILT). He was a member of the PPR WG Probabilistic Methodology Workgroup and contributor to two opinions. He was also lead author of an external report[45] on the same subject, which was mandated by EFSA due to a self-request by the chair of the PPR commission. RIKILT was granted €98.867,51 for this research. Given the position of van Klaveren at EFSA, he clearly has dual roles, being a WG member and contract researcher.

Van Klaveren worked as a researcher for food safety assessment for many years, with a strong focus on probabilistic risk assessment, inspired by the guidance document on probabilistic modelling from ILSI[46]. He shows a heavily biased point of view for promoting a conservative probabilistic approach. He claims that new methodologies won't identify more risk to the public health, since the deterministic model is "black-white"[47] and uses the precautionary principle.[48] He has published several times with ILSI affiliated authors, most notably Juliane Kleiner, then still working for ILSI[49], and most recently gave a presentation at an ILSI Europe workshop called "Guidance for Dietary intake Exposure Assessment".[50]

As the leader of the FP7 project ACROPOLIS, which is co-managed by Freshfel, the European Fresh Produce Association, he maintains strong ties with industry (Freshfel, Bayer, BASF, Syngenta) and ILSI affiliated persons (Boobis, Kleiner, Moretto). ACROPOLIS was selected by the European Commission to address their concerns about the combined exposure to pesticides and given a total sum of approximately three million Euro's.[51, 52]

Van Klaveren states that the research of ACROPOLIS "contributes to the development of a methodology to ensure that the missing aspects [cumulative and synergistic effects] in the risk assessment of pesticides can be addressed in future risk management", but acknowledges that the project is primarily meant to develop new measures, tests and tools for the industry and regulators "to prove that pesticide use is safe"[53]. Furthermore, one of the expected outcomes of ACROPOLIS is to help "convince major food retailers to refrain from introducing unscientific criteria to deal with the issue in response to increased public scrutiny". This precautionary criteria was introduced by several European supermarkets due to the lack of legal progress and public health concerns.

45. Klaveren et al (2009). Cumulative Exposure Assessment of Triazole Pesticides, see www.efsa.europa.eu/en/supporting/pub/40e.htm

46. ILSI (2002). Towards harmonised guidance on applying probabilistic methods to assess operator exposure to plant protection products. Cited in RIKILT (2004). Probabilistic intake calculations performed for the Codex Committee on Pesticide Residues, see http://edepot.wur.nl/36066. Van Klaveren was project leader and co-author for this RIKILT report.

47. www.acropolis-eu.com/object_binary/o4683_SAB_01Klaveren.pdf

48. www.acropolis-eu.com/object_binary/o4422_ACROPOLIS_03.pdf

49. www.ncbi.nlm.nih.gov/pubmed/11893401, http://www.ncbi.nlm.nih.gov/pubmed/21338654

50. www.ilsi.org/Europe/Documents/GUIDEA%20WS%202011/ILSI%20Workshop%20Report%20Brief_v-final-colour.pdf

51. http://cordis.europa.eu/projects/rcn/94836_en.html

52. See topic KBBE-2009-2- 4-03 "Combined exposure to pesticides" in http://ec.europa.eu/research/participants/portal/ShowDoc/Extensions+Repository/General+Documentation/All+work+programmes/2009/Cooperation/b_wp_200901_en.pdf

53. /www.acropolis-eu.com/object_binary/o4422_ACROPOLIS_03.pdf

JULIANE KLEINER

Juliane Kleiner has worked for EFSA since 2004 and has recently been given the position of Director of Science Strategy and Coordination, giving her control over EFSA's science strategy.[54] Although see states nothing about it in her DoI[55], she has worked seven years for industry lobby group ILSI as 'senior scientist', a clear case of 'revolving doors'. She was 'responsible staff scientist' of several ILSI task forces, one of which was the 'risk assessment of chemicals in food'. From 2000 until 2003, Kleiner was ILSI-coordinator of the EU funded program FOSIE on risk assessment of chemicals in food and diet.[56] EFSA's new science director therefore has actively supported and publicly defended industry positions on risk assessment and published opinions together with many industry employees.[57]

After Kleiner started working for EFSA in 2004, she immediately focused on cumulative risk assessment of pesticides. In 2004 she attended the WHO meeting on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals, which was also attended by her former employer ILSI and other industry lobby groups such as ECETOC and industry consultant Bette Meek (see Chapter 4). At the meeting Kleiner also highlighted industry proposals on pesticides.[58]. In 2006 she was present on EFSA's colloquium on cumulative risk assessment[59] and in 2007 attended a WHO/IPCS workshop on combined exposures to multiple chemicals[60] and a WHO/IPCS meeting on Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals[61]. Furthermore, she recently presented the European perspective on risk assessment on the Second ACROPOLIS Stakeholder Conference in October 2013. The fact she keeps on promoting the same industry proposals and keeps on working and publishing with the same industry-linked people is an indication she didn't change her mind when moving form ILSI to EFSA[62].

54. www.efsa.europa.eu/en/staffdirectory/staff/julianekleiner.htm

55. www.efsa.europa.eu/en/staffdirectory/docs/doikleiner.pdf

56. http://cordis.europa.eu/projects/rcn/52359_en.html and www.ilsi.org/Europe/Pages/FOSIE.aspx

57. www.pan-europe.info/News/PR/130910_PANE_who%20is%20Juliane%20Kleiner.pdf

58. www.who.int/ipcs/methods/harmonization/organization/final_report.pdf

59. The EFSA's 7th Scientific Colloquium Report - Cumulative Risk Assessment of pesticides to human health: The Way forward (www.efsa.europa.eu/en/supporting/pub/117e.htm)

60. www.who.int/ipcs/methods/harmonization/areas/aggregate/en/

61. www.who.int/ipcs/methods/harmonization/hsceight_report.pdf

62. www.pan-europe.info/News/PR/130910.html

ALAN BOOBIS

Professor Alan Boobis is connected to the Imperial College London and was EFSA PPR member from 2003-2009. He contributed to two cumulative opinions and was part of EFSA's Cumulative Assessment Groups of Pesticides Workgroup, until June 2012, being forced to leave due to EFSA's more stringent rules on conflicts of interest[63]. Boobis also was a participant of the EU funded research programs BRAFO[64] and ACROPOLIS[65], both of which include industry involvement.

Boobis was chair of the ILSI board of trustees and a fierce defender of industry's agenda in his work. A Science Direct search on his publications reads like a list of ILSI-opinions and ILSI meeting reports. It gives the impression that Boobis is a ILSI ghost writer [66].

Boobis was also heavily involved in the ILSI RISK21 endeavour[67] and published for ECETOC and attended their workshop, although he didn't mentioned the latter in his DoI.[68] He has published a multitude of articles with industry.[69]

At the same time Boobis has been active in EFSA for years and has been allowed to defend industry agenda there.

63. www.efsa.europa.eu/en/press/news/120305.htm

64. http://cordis.europa.eu/projects/rcn/81234_en.html and www.ilsi.org/Europe/Documents/P_BRAFO.pdf

65. In Scientific Advisory Board

66. PAN report on TTC

67. RISK21 Steering Team, Overall Project Co-chairs and Committee Leader, http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=3492; 2010 (May) HESI Annual - Presentation with industry in Workshop, http://www.hesiglobal.org/files/public/2010%20Annual%20Meeting/Presentations/SOS/Risk21_HESI_AMDraft_05-11-10.pdf ; 2012 (June) HESI Annual - Presentations "Risk Assessment for the 21st Century: RISK21 Session Overview and Introduction

68. Participant at ECETOC Workshop Combined Exposure to Chemicals (2011), http://www.ecetoc.org/uploads/Documents/Combined%20Exposure%20WS%20Booklet.pdf. For his publications for ECETOC, see http://www.ecetoc.org/uploads/Publications/ECETOC%202010%20Annual%20Report.pdf"

69. Long list of opinions, 'reviews' and other secondary literature generally being an expression of industry agenda like MoE (with BASF, Syngenta, Astra Zeneca), thresholds, human relevance, (absence of) synergy (with Dow, Bayer, Exxon, Procter & Gamble), cumulative RA , biomarkers , MoA/use of statistical methods , , in vitro tests with Unilever and Sudzucker. In some articles he explicitly declares he has no financial conflicts, even though these commentaries are sponsored by ILSI corporations. Published with Galli, Moretto, Meek, Dellarco, Tritscher, Schlatter, Gundert-Remy and many others with a link to industry.

ANDY HART

Dr Andy Hart is a civil servant working for the British Food and Environment Research Agency (FERA/DEFRA). He's been a PPR member from 2003-2012, chair of the PPR Working Group on probabilistic methodology for dietary exposure assessment, contributor to three opinions and one external report – which was mandated by an internal EFSA request[70].

According to his DoI, Andy Hart has multiple close ties with industry. He's been a long time member of several ILSI working groups[71]. He also attended ILSI[72] and ECETOC[73] workshops and a SETAC conference[74], in all instances; he has failed to mention these issues in his DoI. Furthermore, he received funding from and/or was affiliated to industry co-funded EU projects, including ACROPOLIS[75]. In his DoI he also mentions being a member of the WHO/IPCS Drafting Group for a guidance document on characterising and communicating uncertainty and variability in hazard assessment (as of 2010), but fails to declare his membership of the WHO/IPCS Working Group on Uncertainty in Exposure Assessment[76].

Andy Hart is not an active researcher and publishes with Alan Boobis (strong ties with ILSI), Nestle, Procter &Gamble and ILSI. As such, he's suspected to have a bias towards industry.

70. Glass et al (2012). Collection of the state of the science on combined actions of chemicals in food through dissimilar modes of action and proposal for science-based approach for performing related cumulative risk assessment

71. Member of the Expert Group "Data Selection for Benchmark Dose (BMD) Modelling of Substances that are Genotoxic and Carcinogenic"; 2009-2012, Member of ILSI-Europe Working group on data for benchmark dose modelling; 2005-2007, Member of ILSI Expert Group on Exposure Assessment from Food Contact Materials, developing guidance document.

72. On 11 June 2012 he attended the first meeting of a new ILSI-Europe Expert Group on 'Effectiveness of Exposure Mitigation Options' which is an initiative of the ILSI-Europe Task Force on Process-Related Compounds and Natural Toxins.

73. In parallel with the ECETOC task force, Unilever initiated an exploration of the ICE (Interspecies Correlation Estimation) method in collaboration with Andy Hart. The following Unilever post-doc project was later adopted as an ECETOC task force project (http://www.ecetoc.org/uploads/Publications/ECETOC%202009%20Annual%20Report.pdf).

74. http://setac.eu/embed/downloads/AM09_Scientific_Programme.pdf

75. 008-2012: CEPE funding as part of the EU FP7 project FACET. CEPE represents the interests of paint, printing ink and artists' colours companies at European level; Part of FERA's research team for the FP7 ACROPOLIS

76. www.who.int/ipcs/methods/harmonization/areas/uncertainty%20.pdf

ANGELO MORETTO

Angelo Moretto is an Italian professor working for the University of Milan and the International Centre for Pesticides and Health Risk Prevention (ICPS), which also supplies services to companies.[77] He was a PPR member from 2003-2011, but was removed from the EFSA panel because of undeclared industry connections. During his time at EFSA, he contributed on two opinions on cumulative, one external report and visited several workshop of EFSA, WHO/IPCS and ECETOC on cumulative. Moretto continued to be a member of the PPR WG Cumulative Assessment Groups of Pesticides until June 2012, but has been forced to also give up this position due to stricter EFSA guidelines regarding conflicts of interest.[78]

Moretto worked for ILSI as a member of the ACSA project on testing strategy of Pesticides and was co-chair of the sub-team on Assessment of cumulative exposure to chemicals of ILSI/HESI project RISK 21. He is 17% owner of the company Melete[79], which coordinates activities related to risk assessment of workers exposed to industrial chemicals. He also received funding from Dow AgroSciences, Syngenta and Bayer CropScience and had done consulting work for several other businesses. Furthermore Moretto is Work Package leader of ACROPOLIS for his university and Member of a Scientific Advisory Body of the WHO.

Although Moretto has published with pesticide company employees such as Syngenta, Monsanto, Bayer, and BASF and also industry affiliated persons such as Boobis[80], he is not an actively publishing scientist.

77. www.icps.it/

78. www.efsa.europa.eu/en/press/news/120305.htm

79. www.meletenet.it/english/

80. For example Alan R. Boobis, Bernadette C. Ossendorp, Ursula Banasiak, Paul Y. Hamey, Istvan Sebestyen, Angelo Moretto, Cumulative risk assessment of pesticide residues in food, Toxicology Letters 180 (2008) 137–150 and Doe JE, Boobis AR, Blacker A, Dellarco V, Doerrer NG, Franklin C, Goodman JI, Kronenberg JM, Lewis R, Mcconnell EE, Mercier T, Moretto A, Nolan C, Padilla S, Phang W, Solecki R, Tilbury L, van Ravenzwaay B, Wolf DC., A tiered approach to systemic toxicity testing for agricultural chemical safety assessment., Crit Rev Toxicol. 2006 Jan;36(1):37-68.

IAN DEWHURST

Dr. Ian Dewhurst is a civil servant for the Pesticides Safety Directorate (PSD) in the United Kingdom. Although he wasn't a member of the PPR panel, he contributed on two EFSA opinions on CRA. He acted as co-rapporteur for ILSI on the workshop of the Threshold of Toxicological Concern[81], but didn't mention this in his DoI. He also failed to mention his participation on an ECETOC organised symposium.[82]

Moreover, he participated in the ILSI HESI Risk Assessment in the 21st Century Project (RISC21) Steering team, which aims to model risk assessment along the lines of industry interests and cost reduction. Since 1996 Dewhurst is also a Temporary advisor to WHO panel of JMPR, preparing working documents on various pesticides and contributing to discussion on the derivation of reference doses.

81. http://toxforum.org/participant/ian-dewhurst-chemical-regulation-directorate

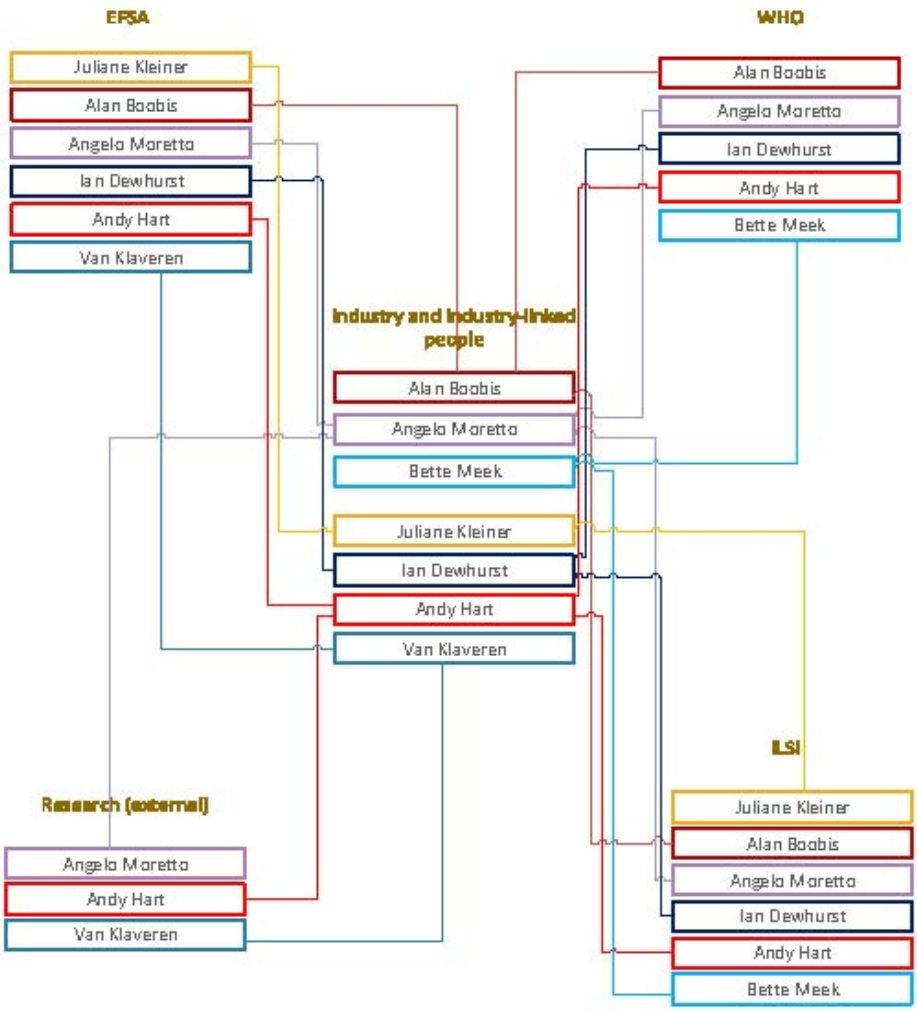
82. www.ecetoc.org/uploads/Publications/ECETOC_2011_Annual_Report.pdf

CONCLUSION

Many EFSA contributors on cumulative risk assessment are connected with industry. Seven of the EFSA contributors had a dual role by simultaneously carrying out different roles: giving "independent" scientific opinion at EFSA and at the same time giving their own advises 'double weight' in EU programs such as Acropolis. As of June 2012, probably due to the new EFSA guidelines of conflicts of interest, one of the most industry-linked persons (*Boobis*) was forced to give up his position at EFSA. Another ILSI-linked person, Moretto, was dismissed for failure to reveal his conflicts of interest[83].

83. EOS, Europe's pesticide and food safety regulators, www.pan-europe.info/Resources/index.html

FIGURE 1 INDUSTRY PLACES ITSELF AT THE HEART OF BRUSSELS DECISION MAKING



6.

THE RESEARCH PROGRAMS OF EFSA AND EU RELATED TO CUMULATIVE RISK ASSESSMENT

We analysed EFSA and EU research programmes on conflicts of interests, industry-links, and dual roles. The EFSA research regarding cumulative assessment[84] however didn't reveal many irregularities, conflicts of interest or a significant number of dual roles. The EU research framework programs do however, and to a great extent. We could imagine the EU research programmes have more flexibility for industry involvement and biased science since cooperation is encouraged in these programs, while the EFSA grants are much more focussed on a special need of EFSA and have a clear term of reference. We also cannot exclude that EFSA used a more stringent policy on avoiding conflicts of interest.

In this chapter, PAN Europe therefore mainly examines the connections between EU funded research programs ACROPOLIS and FOSIE, as these programs are designed to push industry's agenda on cumulative risk assessment.

84. DTU (2012). Identification of Cumulative Assessment Groups of Pesticides; Kortekamp et al (2012). Investigation of the state of the science on combined actions of chemicals in food through dissimilar modes of action and proposal for science-based approach for performing related cumulative risk assessment; Glass et al (2012). Collection of the state of the science on combined actions of chemicals in food through dissimilar modes of action and proposal for science-based approach for performing related cumulative risk assessment; RIA (2013). Toxicological data analysis to support grouping of pesticide active substances for cumulative risk assessment of effects on liver, on the nervous system and on reproduction and development; Klaveren et al (2010). Cumulative Exposure Assessment of Triazole Pesticides; FERA (2009). Cumulative Exposure Assessment of Triazole Pesticides

ACROPOLIS

The ACROPOLIS[85] program is co-managed by the European food traders organisation Freshfel and is focused on the so-called 'probabilistic risk assessment' of mixtures of pesticide residues in food. ACROPOLIS was granted approximately three million euro's from the EU research Framework program to develop a tool to establish safe levels for the daily mixture of pesticide residues in food to which all European consumers are exposed. But as mentioned in the previous chapter, project leader Jacob van Klaveren –with strong ties to industry and EFSA - acknowledges that the project is primarily meant "to prove that pesticide use is safe"[86].

85. Aggregate and Cumulative Risk Of Pesticides: an On-Line Integrated Strategy (ACROPOLIS), www.acropolis-eu.com/

86. www.acropolis-eu.com/object_binary/o4422_ACROPOLIS_03.pdf

Probabilistic risk assessment is a statistical tool calculating the probability consumers have to exposure to a too high dose of a combination of pesticide residues. It is based on unrealistic assumptions such as that people buy food in every shop in their entire country(the tool bases itself on the entire residue analysis database of a country). The tool conveniently allows for some consumer exposure above safety limits without protection

(the statistical curve has a cut-off in the high exposure region). Exposing people to unsafe levels of pesticides is a violation of the pesticides Regulation providing that pesticides "shall not have any harmful effects on human health, and in particular vulnerable groups" (*Art.4*). The tool advocated for by the food traders would mean that combination effects of pesticides (cumulative effects) can be easily qualified as acceptable and the provision in the Regulation to protect people against mixture effects turned into a 'dead letter'.

The ACROPOLIS-program shows both several 'dual roles' of people involved as well as their links to industry. The same experts in panels of EFSA *(see Chapter 5)* have a prominent role in this program while they are clearly linked to industry and industry lobby group ILSI. The program is managed by Jacob van Klaveren. He was first part of the EFSA working group advocating the use of the 'probabilistic risk assessment' tool and now is taking advantage of his own proposal: a clear case of 'dual roles'. Van Klaveren has close ties with industry and ILSI. More people who are part of the EFSA-panels on cumulative, most of which have strong links to industry, are also involved in the ACROPOLIS program, such as Angelo Moretto (*Work Package leader*), Alan Boobis (*Scientific Advisory Board*), Andy Hart (*research on behalf of FERA*), Bernadette Ossendorp (*Work Package Leader*), David Miller (*External Advisory Board*) and Paul Hamey (*participant*). Remarkably, Juliane Kleiner is also associated with the project, as an official representative from EFSA on the Stakeholder Conference in October 2013.[87]

87. http://ec.europa.eu/research/bioeconomy/pdf/acropolis-stakeholder-conference-agenda-15102013_en.pdf

FOSIE

FOSIE[88] was a program that from 2000 until 2003 was focused on qualitative and quantitative methodologies for risk assessment of chemicals in food and diet.[89] It was co-funded for a total sum of €754 thousand euro by the European Commission.[90] It was managed completely by ILSI, with Juliane Kleiner as Scientific Supervisor, now EFSA's Director of Science Strategy

88. Food Safety In Europe: Risk Assessment of Chemicals in Food and Diet (FOSIE)

89. www.ilsi.org/Europe/Pages/FOSIE_Overview.aspx

90. http://cordis.europa.eu/projects/rcn/52359_en.html and www.ilsi.org/Europe/Pages/FOSIE.aspx

and Coordination[91]. FOSIE's Steering Committee was chaired by Unilever, while many other food companies were committee members[92] or partners.[93]

From the start, a probabilistic approach to risk assessment was FOSIE's main objective[94]. As part of the FOSIE project, individual theme groups (ITG) were identified, which produced several publications.[95] Kleiner was co-author of all these publications, while in addition to industry, other authors were van Klaveren, Boobis and industry consultant Susan Barlow, who later became known for changing conclusions in her work for tobacco multinational Philip Morris.[96] In the final publication 'Risk characterisation of chemicals in food and diet', in addition to industry, again Kleiner, Boobis and Barlow contributed.[97]

The document,

- promotes and summarises several industry positions on risk assessment such as the presence of no-effect thresholds, even for carcinogens,
- proposes creating a high burden for regulators by demanding that the mechanism of action is known in case of adverse effects,
- and advocating a range of industry-developed tools to qualify adverse effects from animal studies as acceptable (historical control data, human relevance, threshold of toxicological concern).

The probabilistic risk assessment is highlighted in the document and is another industry invention to consider excesses of food standards as acceptable.

In this case, the EU framework program was used as a tool for industry to push their agenda. A means of getting paid for developing their lobby tools and for creating credibility for ILSI and ECETOC and their tools by suggesting this work is done with contributions from independent scientists.

91. See Chapter 5

92. www.ilsi.org/Europe/Pages/FOSIE_Manage.aspx

93. www.ilsi.org/Europe/Pages/FOSIE_Partners.aspx

94. www.ilsi.org/Europe/Pages/FOSIE_Overview.aspx

95. www.ilsi.org/Europe/Publications/2002Food_Safe-1.pdf

96. Elisa K. Tong, MD; Lucinda England, MD and Stanton A. Glantz, Changing Conclusions on Secondhand Smoke in a Sudden Infant Death Syndrome Review Funded by the Tobacco Industry, PEDIATRICS Vol. 115 No. 3 March 2005

97. www.ilsi.org/Europe/Documents/2002Food_Safe-2.pdf

7.

CONCLUSIONS AND RECOMMENDATIONS

All evidence presented in this report points at a long-term orchestrated industry lobby campaign to turn the policy on cumulative effects of pesticides into a cosmetic procedure with no substantial effects for industry. EU food standards will -if industry gets its way- remain unchanged and the public will get no meaningful protection against the harms of daily exposure to multiple pesticide residues. Industry send out its experts/lobbyist to the international level (WHO) and outnumbered the few other national representatives present. By offering to be part of a steering group or offering to draft the WHO framework, a handful of industry-linked people (Boobis, Meek, Moretto, Kleiner, van Raaij) managed to capture the WHO's work, steering it towards industry's position. It has to be noted that the WHO apparently has no checks and balance to avoid this type of capture by one stakeholder. None of the people who developed the WHO-framework is an active scientist and the majority have never carried out any original research. The scientific quality of the WHO-work on CRA therefore can also be questioned.

Regarding the European Food Authority, a comparable tactic was used by industry. Their experts/lobbyists tried to get seats in EFSA panels and working groups which was made easier by the fact that any policy to stop full industry consultants or people linked to industry lobby groups were lacking in 2004 when EFSA was created. Around 2011 industry seemed to had had the same success with EFSA as they had had with the WHO in imposing their views on policy. It was only through the intervention of DG SANCO that -this time- industry didn't get its way and EFSA was forced to take another road. By that time, six years had already been wasted on useless EFSA opinions and citizens were not protected as required by the 2005 EU-residue Regulation. A delay stimulated by industry representatives. The EFSA pesticide panel apparently kept on resisting the U-turn and EFSA decided in 2012 to terminate their mandate on CRA and EFSA staff worked on it from that time on. EFSA was also very late in acknowledging that conflicts of interest is an issue that needs to be addressed. Addressing conflicts of interest too until 2012 -eight years after the start of EFSA and after intervention by the European Parliament. In the end a policy was adapted. Direct ILSI-ties were not allowed anymore as well as being a full industry consultant. Still many industry-linked people are part of the EFSA panels and the EFSA policy needs to be improved to realise more independent panels.

Many of the same (*industry-linked*) people active in EFSA-panels on CRA gathered in a new EU-research program called ACROPOLIS to

try to include another industry-tool (probabilistic RA) in CRA, led by a food industry lobby group (Freshfel). The very people (Moretto, Boobis, Van Klaveren, Ossendorp, Hart, Meek, Dewhurst, Hamey) who were instrumental in steering EFSA's work towards industry's positions, a mix of industry consultants and captured civil servants.

Our recommendations are for:

a. WHO must revise their CRA recommendations by appointing active scientists without ties to industry

b. WHO must reinforce its independence policy so as to ban conflict of interests

c. WHO to make sure any policy development is done by independent scientists and –if stakeholders are invited- only a balanced stakeholder representation should be allowed

d. WHO must immediately stop collaborating exclusively with industry lobby groups such as ILSI and ECETOC

e. EFSA must strengthen their policy on conflicts of interest and ban them from their panels

f. EFSA must set up more 'check and balances' in the organisation to ensure that any capture from whatever side is prevented

g. EFSA must immediately adapt food standards for pesticide residues to account for the daily mixture of pesticides in food as it can be observed in real life situations

h. The EU must stop allowing industry lobby groups to apply for taxpayers' money in the Framework program and use it to develop industry policy proposals.

i. EFSA must effectively prevent dual roles so that people who have been involved in advising on the introduction of a certain tool are not involved in the development of implementing the tool.

PAN Europe, January 2014

Hans Muilerman, René Houkema

ANNEX I.

PAN EUROPE ANALYSIS OF THE SCIENTIFIC ACTIVITIES OF PEOPLE INVOLVED IN CRA

Name	Active researcher	Suspicious connections in published studies	Apparently industry-linked, paid by industry or clearly serving industry's interests in published studies	Research, example(s) of studies.	PAN Europe qualification of most likely identity
John Christian Larsen, Danish civil servant	No experimental studies published. Few dozen studies published on risk assessment in food, mainly opinions. Active in WHO-panels. No active scientist.	Susan Barlow (consultant cigarette industry & ILSI), Juliane Kleiner (worked for ILSI, now science director EFSA), as an editor to Alan Boobis (ILSI chair)	Industry-linked/ILSI promoted tool TTC	Iona Pratt, Susan Barlow, Juliane Kleiner, John Christian Larsen, The influence of thresholds on the risk assessment of carcinogens in food, Mutation Research 678 (2009) 113–117.	Food contamination specialist
Bette Meek, industry consultant, Canada.	No experimental studies published. Very few publications at all; few opnions published mainly on dose-response discussion in risk assessment. No active scientist. Published several times together with industry representatives, generally on 'mechanisms of action'-ideas which should make it possible to disregard adverse effects found in animal studies such as cancer and serving industry's agenda. Active in WHO/IPCS, unknown basis.	Carmichael (ECETOC), Lewis (Syngenta), Boobis (ILSI), Embry (ILSI), Bausen (BASF), Mellor (AstraZeneca), Rhomberg/Goodman (Gradient, industry consultancy producing desired outcome), Price (Dow), Schitt (Bayer), Gundert-Remy (German BfR, connected to procter & Gamble), Renwick (ILSI)	Serving industry's agenda; likely paid by industry. Also role in defending industry tool 'human relevance' with Meek, Boobis, Schlatter, Olin, Vickers (note parallel; same infiltration group)	I Carmichael, Melanie Bausen, Alan R. Boobis, Samuel M. Cohen, Michelle Embry, Claudia Fruijtier-Pölloth, Helmut Greim, Richard Lewis, M.E. (Bette) Meek, Howard Mellor, Carolyn Vickers, and John Doe, Using mode of action information to improve regulatory decision-making.	Industry consultant.
Damia Barcelo	Managing editor of the journal Science of the Total Environment, no studies published, no scientist	na.	na.		Editor of a journal
Jos Boesten, Alterra, NL	Research on leaching of pesticides to groundwater. Almost 1 article per year active scientists (Dutch Alterra). Involved in EFSA.	Ettore Capri , Theo Brock, Andy Hart, Tony Hardy	No evidence (Alterra gets revenues from pesticide industry, especially Theo Brock on water pollution and mesocosms)		Environmental researcher.
Nena Waight Sharma	No publications. Active in WHO/IPCS. Unknown role.				Australia repres?
Sumol Pavitrannol	No publications. Active in WSHO/IPCS on cumulative! Unknown role.	No author of article Meek/Boobis			Thailand repres?
Carolyn Vickers	Works for WHO, no experimental work, no scientist	Published with ECETOC, ILSI and a range of chemical industries, AstraZeneca, Syngenta, BASF, usual mode-of-action promotion, with Meek/Boobis on cumulative, with Meek/Boobis on human relevance (plus attacking other scientists),	Supports industry views	Boobis AR, Doe JE, Heinrich-Hirsch B, Meek ME, Munn S, Ruchirawat M, Schlatter J, Seed J, Vickers C., IPCS framework for analyzing the relevance of a noncancer mode of action for humans., Crit Rev Toxicol. 2008;38(2):87-96. doi: 10.1080/10408440701749421. Review.	Regulator
Kevin Crofton, US-EPA	Civil servant US EPA, active scientist, active in WHO/IPCS	Article Meek/Boobis	Looks like a decent scientist (puzzling why he signed the Meek/Boobis article)		Scientific advisor EPA
Juliane Kleiner (ILSI/EFSA)	Civil servant at EFSA (science director), used to work for ILSI and defending industry agenda , TTC, risk-benefit RA, carcinogens, etc.	Article with Barlow, Larsen, Pratt defending thresholds/TTC, with Bottex (EFSA also ex-ILSI), Benford (ILSI-connections) and Carlander (moved from EFSA to industry) on risk-benefit. No experimental studies, no scientist.	Industry-linked	Pratt I, Barlow S, Kleiner J, Larsen JC., The influence of thresholds on the risk assessment of carcinogens in food, Mutat Res. 2009 Aug;678(2):113-7. doi: 10.1016/j.mrgentox.2009.05.002. Epub 2009 May 13.	Regulator
Stephen Olin, ILSI	Works for ILSI, the industry lobby club, developing tools and publishing opinions with the aim to get these accepted by regulators. Dozens of published opinions, no experimental studies, no scientist. Active in WHO/IPCS.		Employee industry lobby group (the suggestion many times is given that ILSI is a non-profit neutral scientific institute; they try to involve university professors to help creating this image)	Felter S, Lane RW, Latulippe ME, Llewellyn GC, Olin SS, Scimeca JA, Trautman TD., Refining the threshold of toxicological concern (TTC) for risk prioritization of trace chemicals in food., Food Chem Toxicol. 2009 Sep;47(9):2236-45. doi: 10.1016/ j.fct.2009.06.018. Epub 2009 Jun 14.	Industry lobbyist

Sharon Munn, JRC	Civil servant. Active in WHO/IPCS. Unknown role, now at EU-JRC. No experimental publications, no scientist.	Remarkable connections to Meek/Boobis in defending WHO human relevance tool (Meek, Boobis, Heinrich-Hirsch, Schlatter, Doe -Syngenta- and Olin -ILSI-)	Suspicious.	Meek ME, Berry C, Boobis AR, Cohen SM, Hartley M, Munn S, Olin S, Schlatter J, Vickers C., Re: Guyton, Kathryn Z., Barone, Stanley, Jr., Brown, Rebecca C., Euling, Susan Y., Jinot, Jennifer, Makris, Susan (2008). Mode of action frameworks: a critical analysis. Journal of Toxicology and Environmental Health, Part B, 11(1): 16-31, J Toxicol Environ Health B Crit Rev. 2008 Oct;11(8):681-3; author reply 684-5. doi: 10.1080/10937400801985648.	Regulator
Gerhard Heinemeyer	Civil servant (Germany) on risk assessment. No active scientist. Very few publications. Active in WHO/IPCS on cumulative.	Link to Boobis and Meek on cumulative, link to Gundert-Remy (connection Procter & Gamble) defending TTC, with Carlos Rodriguez (Procter & Gamble) on risk communication.	Industry-linked		Regulator
Claudia Bolognesi	Active scientist. Around 20 publications in the last 5 years, mainly assays on DNA damage.				Clinician
Alan Boobis	UK professor with very few experimental studies published. No active scientist. Active for ILSI (Chair) for many years and he published dozens of opinions for/with ILSI and industry. Mechanism of actions, cumulative, margin of exposure and human relevance are his big targets. Active for many years at EFSA; removed ultimately because of ties with ILSI in 2013. Active in WHO/IPCS.	Long list of opinions, 'reviews' and other secondary literature generally being an expression of industry agenda like MoE (with BASF, Syngenta, Astra Zeneca), thresholds, human relevance, (absence of) synergy (with Dow, Bayer, Exxon, Procter & Gamble), cumulative RA , biomarkers , MoA/use of statistical methods , in vitro tests with Unilever and Sudzucker. In some articles he explicitly declares he has no financial conflicts, even though these commentaries are sponsored by ILSI corporations. Published with Galli, Moretto, Meek, Dellarco, Tritscher, Schlatter, Gundert-Remy and many others with a bias.	Industry linked for > 10 years	Boobis A, Budinsky R, Collie S, Crofton K, Embry M, Felter S, Hertzberg R, Kopp D, Mihlan G, Mumtaz M, Price P, Solomon K, Teuschler L, Yang R, Zaleski R., Critical analysis of literature on low-dose synergy for use in screening chemical mixtures for risk assessment, Crit Rev Toxicol. 2011 May;41(5):369-83. doi: 10.3109/10408444.2010.543655. Epub 2011 Feb 10. Review.	
Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Raaij MV, Vickers C., Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework, Regul Toxicol Pharmacol. 2011 Apr 2. [Epub ahead of print]	Industry consultant				
Arne Buchert	No publications.				
Ettore Capri	Capri coordinates the OPERA FP7 programme, designed to undermine Integrated Production and give pesticides a 'green' image. Close cooperation with industry. He is an active scientists publishing on environmental studies, pesticides, dioxins in milk and biobeds and such. Publishes with chemical industry and engaged in FP7 programmes with industry.	Denying problems with pesticides for Syngenta (Fabio Berta, Roberto Bassi), also on the soil fumigant Dichloropropene for Dow (Steve Kennedy), same for the persistent pesticide Quinoxyfen for Dow (Graham Reeves, Giovanna Meregalli) as well as for Chlorpyrifos with Dow, (Graham Reeves)	Generally favourable outcome for industry.	Calliera M, Berta F, Galassi T, Mazzini F, Rossi R, Bassi R, Meriggi P, Bernard A, Marchis A, Di Guardo A, Capri E, Enhance knowledge on sustainable use of plant protection products within the framework of the Sustainable Use Directive, Pest Manag Sci. 2013 Aug;69(8):883-8. doi: 10.1002/ps.3579. Epub 2013 Jun 12.	Active scientist and industry consultant

Angelo Moretto	Italian neurotoxicity scientist with very few experimental studies. No active scientist. Mainly producing opinions and 'reviews' in journals. Active in ILSI, active in EFSA (removed for not declaring conflicting interest), active in WHO/IPCS and linked to research programmes such as Acropolis. Double role.	Publishing with pesticide company employees, Syngenta, Monsanto, Bayer, BASF, Boobis,	Mixed. Industry connections in the collaboration with ILSI; unsure mission. But also neutral studies published on neurotoxicology and for instance Parkinson.	Alan R. Boobis, Bernadette C. Ossendorp, Ursula Banasiak, Paul Y. Hamey, Istvan Sebestyen, Angelo Moretto, Cumulative risk assessment of pesticide residues in food, Toxicology Letters 180 (2008) 137–150 Doe JE, Boobis AR, Blacker A, Dellarco V, Doerrer NG, Franklin C, Goodman JI, Kronenberg JM, Lewis R, Mcconnell EE, Mercier T, Moretto A, Nolan C, Padilla S, Phang W, Solecki R, Tilbury L, van Ravenzwaay B, Wolf DC., A tiered approach to systemic toxicity testing for agricultural chemical safety assessment., Crit Rev Toxicol. 2006 Jan;36(1):37-68.	Specialist on neurotoxicology
Bernadette Ossendorp	Civil servant at Dutch RIVM. No experimental studies published in recent years, no active scientist. Chair EFSA pesticide PPR panel.	Through EFSA on TTC with Boobis, on reduction animal testing with Aldert Peirsma (ILSI connection)	Supports industry views	Alan R. Boobis, Bernadette C. Ossendorp, Ursula Banasiak, Paul Y. Hamey, Istvan Sebestyen, Angelo Moretto, Cumulative risk assessment of pesticide residues in food, Toxicology Letters 180 (2008) 137–150	Regulator
Walter Steurbaut	Works for Gent University and Belgium institute ILVO, plant protection. Steurbaut works on exposure to pesticides. Commercial contracts possible. Few experimental studies, no active scientist. Involved in EU programmes (Capri, OPERA) and EFSA tenders. Double roles.	No evidence	No evidence for studies		Bio-monitoring specialist
Maria Taheva	Not present in public journals				
Christiane Vleminckx	Not present in public journals				
Ursula Banasiak	Civil servant at German risk assessment institute. No active scientist. Active in EFSA on cumulative.	Only via EFSA (Boobis, Moretto, Ossendorp)	Together with Gundert Remy questioning European policy on zero tolerance of chemicals, likely biased	Alan R. Boobis, Bernadette C. Ossendorp, Ursula Banasiak, Paul Y. Hamey, Istvan Sebestyen, Angelo Moretto, Cumulative risk assessment of pesticide residues in food, Toxicology Letters 180 (2008) 137–150	Regulator
Ian Dewhurst	UK civil servant on risk assessment. No scientist. Collaborates open and freely with industry. Active in WHO	Published opinions on reduction animal testing with Dow, Huntington Life Sciences, on stopping mouse testing with Dow (Richard Billington), Syngenta (Richard Lewis),	Industry-linked; opposes regulating companies	Billington R, Lewis RW, Mehta JM, Dewhurst I, The mouse carcinogenicity study is no longer a scientifically justifiable core data requirement for the safety assessment of pesticides, Crit Rev Toxicol. 2010 Jan;40(1):35-49. doi: 10.3109/10408440903367741. Review.	Regulator
Paul Hamey	civil servant at UK PSD. No original articles published,. No active scientist. Involved in EFSA on cumulative	No evidence (apart from the EFSA group	Supports industry views	Alan R. Boobis, Bernadette C. Ossendorp, Ursula Banasiak, Paul Y. Hamey, Istvan Sebestyen, Angelo Moretto, Cumulative risk assessment of pesticide residues in food, Toxicology Letters 180 (2008) 137–150	Regulator
Andy/Andrew Hart	civil servant at UK Fera. No active scientist. Few publications on benefit-risk assessment. Active in FP7 Browse on exposure of pesticides, active in EFSA. Double roles.	With Boobis on margin of exposure, on BRAFO with Nestle (Benoit Schilter), Procter &Gamble (Katrin Schutte), ILSI (Allessandro Chiodini).	Follows the money, industry-linked	Nienstedt KM, Brock TC, van Wensem J, Montforts M, Hart A, Aagaard A, Alix A, Boesten J, Bopp SK, Brown C, Capri E, Forbes V, Köpp H, Liess M, Luttik R, Maltby L, Sousa JP, Streissl F, Hardy AR, Development of a framework based on an ecosystem services approach for deriving specific protection goals for environmental risk assessment of pesticides, Sci Total Environ. 2012 Jan 15;415:31-8. doi: 10.1016/j.scitotenv.2011.05.057. Epub 2011 Jul 6.	Regulator

Jacob van Klaveren (Rikilt/RIVM – NL)	Civil servant at Dutch Rikilt institute, later RIVM. Few statistical studies; no active scientist. Focussed on one single tool: probabilistic risk assessment. Active in EFSA and FP7 research programmes (double role)	No evidence	Promoting his tool, industry-linked		Regulator
Susan Barlow	Consultant for industry and ILSI, active in EFSA but removed due to ILSI-connections, scientific misconduct in the past for cigarette industry, no experimental studies, no scientist	Schlatter, Boobis, Galli, Knaap, etc.	Defending industry interests		Industry consultant
Diane Bedford	UK civil servant, strong connections to industry and ILSI, active in EFSA	On margin of exposure with Unilever, Nestle, Schlatter, Renwick (both ILSI-linked)	Industry linked	Benford D, Bolger PM, Carthew P, Coulet M, DiNovi M, Leblanc JC, Renwick AG, Setzer W, Schlatter J, Smith B, Slob W, Williams G, Wildemann T., Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic, Food Chem Toxicol. 2010 Jan;48 Suppl 1:S2-24. doi: 10.1016/j.fct.2009.11.003. Review.	Regulator
Corrado Galli	Italian professor and immunologist. Active scientist. Active in EFSA, long relation with ILSI, defends as a lobbyist the very harmful pesticide Vinclozolin. Double roles.	Yes, on TTC with Kroes, Renwick, Boobis, also Unilever, Dow, ILSI, Coca-Cola	Industry linked.	Koster S, Boobis AR, Cubberley R, Hollnagel HM, Richling E, Wildemann T, Würtzen G, Galli CL., Application of the TTC concept to unknown substances found in analysis of foods, Food Chem Toxicol. 2011 Aug;49(8):1643-60. doi: 10.1016/j.fct.2011.03.049. Epub 2011 Mar 30. Review.	Scientist and industry consultant.
Ursula Gundert-Remy	German professor and active scientist. Also works for German BfR which is known to be very industry-friendly. ILSI-advisor 2005-2010, active in EFSA.	Yes, on TTC, with Procter & Gamble, Unilever and Nestle, also Boobis, Piersma.	Industry linked		Clinician
Marcel van Raaij	Civil servant at Dutch RIVM. No active scientist. Active in WHO/IPCS	Defending thresholds with Piersma (ILSI connection), Vermeire, Van Leeuwen and Knaap (connection Unilever), with Boobis and Meek on cumulative, with Dewhurst (UK), Dellarco (EPA and Tritscher (WHO) on reference doses.	Industry linked	Piersma AH, Hernandez LG, van Benthem J, Muller JJ, van Leeuwen FX, Vermeire TG, van Raaij MT., Reproductive toxicants have a threshold of adversity., Crit Rev Toxicol. 2011 Jul;41(6):545-54. doi: 0.3109/10408444.2011.554794. Epub 2011 May 24.	Regulator
Carlos Rodriquez	Employee Procter & Gamble, active for ILSI (WHO)	No publications	Industry employee		Employee Procter & Gamble
Josef Schlatter	Swiss civil servant, served in ILSI Board and many expert groups	With ILSI, Barlow, Benford, Kleiner, Dybing, Renwick, Bridges, Edler, Knaap, Kroes, Boobis, Doe, Meek, Heinrich-Hirsch and many other industry-linked people	Industry linked	Benford D, Bolger PM, Carthew P, Coulet M, DiNovi M, Leblanc JC, Renwick AG, Setzer W, Schlatter J, Smith B, Slob W, Williams G, Wildemann T., Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic, Food Chem Toxicol. 2010 Jan;48 Suppl 1:S2-24. doi: 10.1016/j.fct.2009.11.003. Review	Regulator

ANNEX II.

ANALYSIS OF THE DECLARATIONS OF INTEREST AND PUBLIC INFORMATION REGARDING CONFLICTS OF INTERESTS OF PEOPLE IN EFSA PANELS (INCLUDING OBSERVED OMISSIONS)

Name	Profession	Link with ILSI and industry lobby groups according to the Declaration of Interests (DoI) and/or consultancies	Link with industry according to the Declaration of Interests (DoI) and/or consultancies
Alan Boobis	Professor and industry consultant	Yes, chair of Board of trustees and member of Board of Directors; also a range of consultancies for ILSI, ECETOC and CEFIC and EU-funded programs of ILSI	Yes, consultancies for many chemical companies, AstraZeneca, Sumitomi, GlaxoSmithKline. Scientific Advisory Board ACROPOLIS.
Alberto Mantovani	Professor	Visited an ILSI and a CEFIC meeting.	No
Andreas Kortenkamp	Professor	No	No
Andy/Andrew Hart	Civil servant	Yes, member of two different ILSI expert groups; also member of new ILSI expert group 'Effectiveness of Exposure Mitigation Options' (not in his DoI)	Yes, consultancy for CEPE, flavouring industry; work for ACROPOLIS (not in his DoI).
Angelo Moretto	Professor	Yes, member of two different ILSI expert groups	Yes, consultancy for Syngenta, Dow and several other companies. Owns 17% of Melete, a risk assessment company. WorkPackage leader ACROPOLIS
Anita Stromberg	Civil servant	No	No
Annette Petersen	Civil servant	No	No
Antonio F. Hernandez	Professor	No	Member of the National Scientific Committee of the IUTOX 2010 Congress, with members as BASF, Syngenta
Arne Büchert	Civil servant	No	No
Bernadette Ossendorp	Civil servant	No	Through ACROPOLIS (Freshfel)
Christiane Vleminckx	Civil servant	No	No
Claudia Bolognesi	Researcher	No	No
David Miller	Civil servant US-EPA	No	Shares of Pfizer and IHoneywell. ; ACROPOLIS external advisory board (not in his DoI)
Ettore Capri	Professor and industry consultant	Yes, cooperation with ECPA, 2011: provided additional research support for ILSI report [not in his Doi], http://edepot.wur.nl/193177	Yes, cooperation with many companies in OPERA and consultancies for chemical companies
Ian Dewhurst	Civil servant	No, but 2011, published about ILSI TTC workshop [Not in DoI]	No
Jacob Klaveren	Civil servant	No, but 2011, presentation on ILSI Europe Workshop Guidea - On Guidance for Dietary intake Exposure Assessment, http://www.ilsi.org/Europe/Documents/GUIDEA%20WS%202011/ILSI%20Workshop%20Report%20Brief_v-final-colour.pdf [not in DoI]	As Project Coördinator ACROPOLIS.
Juliane Kleiner	Civil servant	Nothing on her 7 years for ILSI; only mentioning one contact with an ILSI/project EURRECA	No
Karen Ildico Hirsch	Civil servant	No	No
Kyriaki Machera	Civil servant / consultant	Expert for ECPA Operator and Resident Exposure and Risk Assessment, as part of BROWSE FP [DoI] , and 2012 attended 6th SETAC World Congress / SETAC Europe 22nd Annual Meeting, http://berlin.setac.eu/?contentid=404 [not in DoI]	No (agri institute)
Maria Tasheva	Civil servant, retired	No	No
Mark Montforts	Civil servant	SETAC: 2002-now, Session chair on several topics: pesticide field studies; emerging contaminants; medicines." [DoI]	No
Markus Müller	Consultant	No	No
Paul Hamey	Civil servant	No, but Submitted report to ILSI Risk Sciences Institute Probabilistic worker exposure assessment workshop, http://www.hse.gov.uk/research/rrpdf/rr763.pdf [not in DoI]	Connection with food industry via FP program ACROPOLIS
Roland Solecki	Civil servant	No	No
Susanne Hougaard/Bennekou	Civil servant / consultant	No	No
Ursula Banasiak	Civil servant	No	No
Yolanda Pico	Professor	No	No

ANNEX III.

TECHNICAL BACKGROUND ON THE POLICY REGARDING CUMULATIVE RISK ASSESSMENT AND THE VIEWS OF ACTORS

I.1 INDUSTRY POSITION ON CUMULATIVE EXPOSURE OF PESTICIDES AND CHEMICALS (CEPC)

ILSI

The International Life Sciences Institute (ILSI), an industry lobby group, in 1999 convened a meeting with a group of experts to consider the definition of the term "common mechanism". They concluded that chemicals act via a common mechanism of toxicity if they cause the same critical effect, act on the same molecular target issue, act by the same biochemical mechanism of action, or share a common toxic intermediate[1].

1. Mileson, B.E., Faustman, E., Olin, S., Ryan, P.B., Ferenc, S., Burke, T., 1999. A framework for cumulative risk assessment. In: Mileson, B.E., Faustman, E., Olin, S., Ryan, P.B., Ferenc, S., Burke, T. (Eds.), International Life Sciences Institute. An ILSI Risk Science Institute Workshop Report. pp. 1–55.

FOSIE (ILSI)

FOSIE was a program that ran from 2000 until 2003 and was focused on qualitative and quantitative methodologies for risk assessment of chemicals in food and diet. It was co-funded for a total sum of €754 thousand by the European Commission and managed completely by ILSI. ILSI employee Juliane Kleiner was the Scientific Supervisor and she is now EFSA's Director of Science Strategy and Coordination. FOSIE's Steering Committee was chaired by Unilever, while many other food companies were present as committee members or partners. From the start, a probabilistic approach to risk assessment was FOSIE's main objective.

MORETTO (ILSI/INDUSTRY, WHO, EFSA)

Moretto, an Italian scientist involved in ILSI, shows in his 2008-"review"[2], based on his experience in the EFSA PPR-panel the typical regulator/industry view:

2. Angelo Moretto, how to assess the risk from pesticide residues in food, Trends in Food Science & Technology 19 (2008) S56eS63

"Exposure to multiple pesticide residues derived from food is a common occurrence in the general population. Levels of exposure are usually low, below the effective doses. Interactions, such as potentiation and synergism, are not expected to occur at these doses. Available evidence indicates that risk assessment should be carried out for mixtures containing compounds with the same mode of action, since their effects are expected to cumulate".

Nothing harmful expected, only risk assessment needed for same mode of action. His opinion is not based on much experimental evidence but mainly assumptions.

He states dose-addition (same MOA, same CAG (Common Assessment Group) will occur, while response addition (dissimilar MOA, same endpoint) will "rarely, if ever, occur". And if so, only at higher doses. Conclusion: Only dose-addition of CAG is relevant.

Regarding the criteria for identifying a CAG, a MOA is sufficient (mode-of-action, not mechanism of action -mechanism of action, the exact description of the events in the body, is very rarely known-), the common key events leading to the toxic action. For endocrines this is different, he feels, and here grouping should be done according to a common effect. Since the "data" show that exposure to mixtures doesn't increase the risks, assessment has no priority and research should be focussed on CAG's.

Note Moretto later was expelled from EFSA panels because he kept part of his industry affiliations hidden[3].

3. Representing two institutes, Department of Occupational and Environmental Health, University of Milano, Italy, and International Centre for Pesticides and Health Risk Protection (ICPS), "L. Sacco" Hospital, Milano, Italy

LARSEN (ILSI/INDUSTRY, WHO, EFSA)

Larsen, an ILSI-affiliated civil servant from Denmark, in his 2010-report[4] explains cumulative effects. Elements are similar action (dose-addition), dissimilar action (response addition) and interaction (synergy, antagonism). He feels that overall, interactions appear less often at relatively low exposure levels compared to high exposure levels since they are primarily caused by various thresholds and saturation phenomenon (saturation of activating, detoxification or reparative processes). And based on an experiment with chemicals at their NOAEL (No Observed Adverse Effect Level), they feel exposure levels at or below the individual NOAELs of the compounds in a mixture are therefore not expected to be associated with a greater hazard than exposure to the individual chemicals. Dose addition should only be used for similarly acting chemicals. The review analyses 8 different way of assessing dose-addition. Larsen doesn't like the use of "policy-driven" standards like ADI but prefers NOAEL and BMD10 (benchmark dose 10%).

4. Risk assessment of mixtures of pesticides. Current approaches and future strategies, Trine Klein Reffstrup, John Christian Larsen, Otto Meyer, Regulatory Toxicology and Pharmacology 56 (2010) 174–192

He also promotes a new way, physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modelling. A PBTK model can predict tissue concentrations and true toxicokinetic parameter values under a variety of conditions. It is useful to predict internal dose levels for hypothetical exposure regimens which will reduce the uncertainty in risk assessment. It is also possible to predict overload of toxicokinetic pathways and to do high-dose to low-dose extrapolation. The models are mathematically complex and require extensive data on disposition of the chemical and physiological parameters-related data. In any case, clearly a model about thresholds and reversibility of effects. An 'interaction threshold' is claimed to be visible for two organophosphates below which there is additivity and above this threshold antagonism. Hypothesis and predictions make this model difficult to standardise and subject to expert judgement.

The proposed steps for PBTK are:

(1) Identify toxic effects in animals (and humans) and determine the critical effects.

(2) Search the literature and organise available data in order to determine the mode of action, metabolism, as well as physiological constants for the relevant animal.

(3) Suggest relationships between response and tissue dose.

(4) Model formulation: develop a PBTK model to estimate the tissue dose metric at various doses.

(5) Run the model.

(6) Compare output from the model-simulation with available experimental data. If the result from the simulation deviates from the data go to point (7) otherwise go to point (9).

(7) Refine the model.

(8) Repeat point (5) and (6).

(9) Application in risk assessment.

Likely, for most chemicals data are lacking and PBTK could lead to much speculation.

The approach is also in line with industry attempts to focus more on exposure levels and define a safe level (such as TTC, Threshold of Toxicological Concern).

Larsen claims the EFSA 2008 opinion[5] highly supports PBTK and concludes it is the highest tier of cumulative risk assessment.

5. EFSA, 2008. Scientific opinion of the Panel on Plant Protection products and their Residues (PPR Panel) on a request from the EFSA evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005 (Question No. EFSA-Q-2006-160). EFSA J. 704.

BOOBIS (ILSI/INDUSTRY, WHO, EFSA)

Boobis, an UK professor who spend a big part of his career supporting ILSI (many years chair of board of trustees at ILSI), together with ILSI and industry people from Bayer, Procter & Gamble and Exxon published an opinion on synergetic effects in a scientific journal[6]. Only few studies are available to draw a conclusion and he selected six. After evaluation of the six studies that provided useful quantitative estimates of synergy, the magnitude of synergy at low doses did not exceed the levels predicted by additive models by more than a factor of 4. Only a moderate toxicity increase, according to Boobis. The study also again promotes the use of TTC "as a screening tool" for mixtures to reduce the costs for industry. TTC is a probabilistic tool, allowing 5% of the chemicals to exceed safe levels.

6. Alan Boobis, Robert Budinsky, Shanna Collie, Kevin Crofton, Michelle Embry, Susan Felter, Richard Hertzberg, David Kopp, Gary Mihlan, Moiz Mumtaz, Paul Price, Keith Solomon, Linda Teuschler, Raymond Yang, and Rosemary Zaleski, Critical analysis of literature on low-dose synergy for use in screening chemical mixtures for risk assessment, Critical Reviews in Toxicology, 2011; 41(5): 369–383.

MEEK (ILSI/INDUSTRY, WHO)

Meek, a Canadian scientist with a long history of supporting ILSI, took advantage of her work at IPCS/WHO to write an opinion in a scientific journal[7]. She acknowledges the heavy industry influence: While led by WHO IPCS, the project involved contribution of case studies from the European Centre for Ecotoxicology and Toxicology of Chemicals (*ECETOC, an industry lobby group in Europe*) and the International Life Sciences Institute Health and Environmental Sciences Institute (*ILSI HESI, an international industry lobby group*). While supporting Boobis and ILSI on a strict approach (high barriers for regulators to positively categorise chemicals for cumulative) on cumulative, she tries to show the approach can be used in practice by highlighting the case of PBDE's

7. M.E. (Bette) Meek, International experience in addressing combined exposures: Increasing the efficiency of assessment, Toxicology 313 (2013) 185– 189.

(PolyBrominatedDiphenylEthers). For the group of PBDE's she calculated a maximum intake for babies of 2,6 ug/kg bw. She promotes the use of TTC (cf. TTC safe threshold 1,5 ug/kg bw) as a standard for assessment. While TTC is exceeded this does not indicate a concern, according to Meek, but only the need to do a refinement of the assessment.

I.2 IPCS/WHO POSITION ON CUMULATIVE EXPOSURE OF PESTICIDES AND CHEMICALS (CEPC)

In 2007 an IPCS/WHO workshop was organised, a project conducted within the IPCS project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals, which started in 2004. In 2009 a report[8] was published on the outcome of the workshop. Members of the working group preparing the workshop were: Bette Meek (*workshop Chair*), Alan Boobis, Kevin Crofton, Gerhard Heinemeyer, Sumol Pavitrannon, Carlos Rodriguez, Marcel Van Raaij, Nena Waight-Sharma, European Chemicals Bureau (*Sharon Munn*), European Food Safety Authority (*Juliane Kleiner*) and International Life Sciences Institute (*Stephen Olin*). Note Juliane Kleiner, member management team of ILSI moved in 2004 from ILSI to EFSA. Among the participants[9] are more industry-affiliated persons.

One the proposals launched at the WHO-meeting was that cumulative only counts if there is a common structure -> common metabolite (ADME) -> common molecular target (mechanism considerations) -> common key event (MOA) -> common tissue (response). In a tiered approach in tier 1 dose addition is assumed as worse case and the exposure compared to a NOEL (*by MOE, margin of exposure*). If this would not give an acceptable outcome, one moves to a higher tier. If there is a difference, a chemical can be dropped from the group. The approach/hypothesis is promoted by Boobis (*chair board of trustees of ILSI*).

8. ASSESSMENT OF COMBINED EXPOSURES TO MULTIPLE CHEMICALS: REPORT OF A WHO/IPCS INTERNATIONAL WORKSHOP ON AGGREGATE/CUMULATIVE RISK ASSESSMENT, WHO, 2009

9. P. Michael Bolger, College Park, MD, USA; Alan R. Boobis, London, England; Edith Clarke, Accra, Ghana; Kevin M. Crofton, Research Triangle Park, NC, USA; Vicki Dellarco, Washington, DC, USA; Christopher T. De Rosa, Atlanta, GA, USA; Ian Dewhurst, York, England; Chris Gennings, Richmond, VA, USA; John P. Groten, Oss, Netherlands; Annika Hanberg, Stockholm, Sweden; Gerhard Heinemeyer, Berlin, Germany; John Christian Larsen, Søborg, Denmark; Inge Mangelsdorf, Hanover, Germany; Bette Meek, Ottawa, Canada; Angelo Moretto, Milan, Italy; Moiz Mumtaz, Atlanta, GA, USA; Kevin Park, Liverpool, England; Sumol Pavittranon, Nonthaburi, Thailand; Christopher J. Portier, Research Triangle Park, NC, USA; Trevor Satchwill, Ottawa, Canada; Josef Schlatter, Zurich, Switzerland; Keith R. Solomon, Guelph, Canada; Tania M. Tavares, Salvador, Bahia, Brazil; Linda K. Teuschler, Cincinnati, OH, USA; Marcel T.M. Van Raaij, Bilthoven, Netherlands; Theo Vermeire, Bilthoven, Netherlands; Nena Waight-Sharma, Canberra, Australia.

Several ideas how to cumulate similar effects (HI, TEQ, etc.) were made. Also there was a suggestion to assess cumulative exposure with TTC (*Larsen*).

A Dutch expert (*van Raay*) promoted probabilistic modelling because deterministic would be over conservative; also Boobis adds this is 'extremely' conservative. Probabilistic again allows a percentage of harm.

Linda Teuschler from US-EPA was the only one talking about whole mixtures and dissimilar mode of actions, mentioning dose addition or effect addition as a widely used method of analysis.

The authors like to avoid the internationally agreed standards for human protection such as ADI and substitute it by NOEL or even BMD10 (benchmark dose 10%), and use a MOE (margin of exposure calculation). This approach conveniently gets rid of the standard 10 x10 default uncertainty factors, limiting the chance of having a too high exposure. They also mention TTC which is again relaxing official standards by using probabilistic approach and accepting a percentage of harm.

They next stress the conservative assumptions but forget to mention this is only the first tier which in practice never will be used while the higher tiers are not conservative at all and even have unknown protection. They stress that problems in tier 1 are no reason for a health concern but only to start doing higher tier assessments.

Dose addition is considered enough conservative, and synergistic action rare.

A tiered hazard assessment is proposed, and if they get to a high tier, a probabilistic estimate of risk.

In the industry-case on 10 chemicals in drinking water, the HI was used and TTC as 'safe' dose.

Meek and Boobis after their IPCS/WHO-involvement published an opinion in a scientific journal[10] with the suggestion this is the IPCS/WHO-developed framework for cumulative assessment

10. M.E. (Bette) Meek, Alan R. Boobis, Kevin M. Crofton, Gerhard Heinemeyer, Marcel Van Raaij, Carolyn Vickers, Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework, Regulatory Toxicology and Pharmacology 60 (2011) S1–S14.

while the WHO-workshop in 2007 only presented individual opinions of the attendants. The article mainly puts forward the ILSI/Boobis proposal for risk assessment with a very high burden of proof for regulators to show similar action of chemicals. Two case studies are meant to help creating the impression this is an operational framework. One case study is from Meek on PBDE's, and another from Boobis and a range of industry-people (Dow, ILSI, Procter & Gamble, Bayer and ExxonMobile) on a mixture of substances in surface water. Meek uses a MOE-approach to show there is no harm, while Boobis cs. uses TTC to claim safety. Both examples can only be used because of the data available. For cumulative assessment in general, these cases appear to have hardly any relation to practice since the data for this kind of calculations (except for pesticide residues) and the information on MOA are lacking generally.

I.3 NGO POSITION ON CUMULATIVE EXPOSURE OF PESTICIDES AND CHEMICALS (CEPC).

NGO's such as PAN-Europe favour the use of the precautionary principle according to the EU Treaty and act when there is reason for concern and not wait for years to do additional studies, look for additional methodologies, and give industry limitless opportunities to claim observed effects are irrelevant. The 2005-Residue Directive makes cumulative assessment mandatory BUT only as soon as EFSA comes up with methods to asses the effects. While these methods are available, at least for pesticides with common adverse outcome such as organophosphates and used in the US, it is highly irresponsible to ignore these methods and start from scratch inventing the wheel, and put consumers for many more years at risk.

For the chemicals with a common endpoint (reproduction, endocrine disruption), PAN Europe[11] feels the doses of these chemicals should be added and the strictest ADI taken as the basis of assessment in a deterministic approach of MRLs.

11. PAN Europe position on mixtures 2011.

This however regards only a tiny part of the entire mixture problem. People are exposed to hundreds of chemicals every day and the negative effect on the body should be considered in a holistic way. From a scientific point of view the body is connected and interrelated by three big communication systems. Assuming that effects on a certain part, system or organ has no connection to effects on another part, system or organ is unfounded. PAN Europe therefore proposes to include -on top of the cumulative calculation- an extra uncertainty factor of 10 to account for cumulation of the hundreds of mixture effects on the entire body.

I.4 EFSA POSITION ON CUMULATIVE EXPOSURE OF PESTICIDES AND CHEMICALS (CEPC).

1. SCIENTIFIC COLLOQUIUM 2006[12]

12. EFSA's 7th Scientific Colloquium - Cumulative Risk Assessment of Pesticides to Human Health: the Way forward, 28-29 November 2006 - Parma, Italy, www.efsa.europa.eu/en/events/event/colloque061128.htm

The audience of the meeting was selected by EFSA (invited-only) and while it was crowded with industry representatives (*Syngenta, ILSI, ECPA, Bayer, BASF, etc*) and industry linked people (*Boobis, Galli, Larsen, Moretto, etc.*), representatives from civil society were excluded from the meeting. The claim to have an 'open debate' is far from being realised and the close ties between EFSA and industry once again shown.

The attendants wanted to focus on groups with a common mode-of-action (MOA) and dose-addition and give less attention to other cumulative effects. Very curiously they stated they do not want the groups to be defined by "interest groups". Probabilistic modelling will be discussed as one of the major methodologies in assessment of risks. US-EPA has a quite strict approach on common MOA and only accepts them if the MOA is known. In the EU less mechanistic studies are needed, and a less strict approach could be to use the combined same endpoints.

Ideally, data should be available to

i) define the key events to identify the mode of action;

ii) provide adequate information on the dose-response to allow good estimates of benchmark doses;

iii) identify the time course of effects, for use in acute and chronic assessments;

iv) provide information on representative mixtures.

Also the group mentions:

A long-term goal should be to revise the current toxicity testing paradigm to a risk based and tiered approach that more efficiently obtains targeted data on kinetics/dosimetry, mode of action, and dose response, which will benefit both aggregate and cumulative risk assessments.

A (very) high burden of proof for regulators to act on a pesticide therefore, and this could delay a cumulative assessment for many years or decades.

Groups with a common MOA to be dealt with first are: Organophosphorus (OP) compounds, Carbamates (cholinesterase inhibiting), only acute exposure might need to be considered, and there might be scope for combining the assessment with that for the OPs, Conazoles: there are many compounds within the group, Pyrethroids: the possibility of sub-grouping was considered and note was taken of ongoing research in the USA, Dicarboximides (vinclozolin, procymidone, chlozolinate and iprodione), Microtubule / Spindle inhibitors, Phthalimides (captan and folpet), Dithiocarbamates.

For non dose-addition effects, it starts with this assumption:

The discussion group decided that effect addition is not relevant to consider for mixtures where exposure is below the NOAEL for each individual compound for dissimilar action (while this is not experimentally tested). However synergy and potentiation could be relevant.

The group only considered common MOA and common endpoints. It seems they consider MOA as mutually independent which is a questionable conclusion in an organism that it completely interdependent by the internal communication systems. The group proposes different methods such as the Hazard Index, the percentages of the ADI (exposure/ADI) cumulated. Also industry babies such as 'Benchmark Dose' and 'Margin of Exposure' are mentioned.

Again, the assumption was made that, interaction of compounds with simple dissimilar actions are not of concern at levels below the ADI for all these compounds. Clear favouring of the probabilistic tool for assessing effects (99% percentile). Deterministic only for acute. The final conclusion is that cumulative assessment is possible but only after much research is done, on the right data, on the right methods, on MOA of the chemicals itself and will take (much) time to develop.

2. OPINION ON METHODOLOGIES, 2008[13] (PPR PANEL)

Members were ao. Boobis, Capri, Moretto, Steurbaut.

Ideally all sources should be taken into account, but since only residues in food have good data on exposure, they will limit their selves to pesticides. They next limit themselves to 'dose-addition', because "although toxic interactions from pesticide residues in food cannot be ruled out, there is no empirical evidence for their occurrence at the expected levels of exposure from pesticide residues in food". And conveniently forgetting about current scientific knowledge.

EFSA again shows methods are available for cumulative assessment and used in practice:

- assessments of organophosphorous (OP) insecticides alone (in USA), or

- together with carbamates (in UK, DK, NL), triazines, chloroacetanilides, carbamates alone (in USA), and all compounds (in DE), and deliver comparable results.

13. Scientific Opinion of the Panel on Plant Protection Products and their Residues (PPR Panel) on a request from the EFSA evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005. The EFSA Journal (2008) 704, 1-85

It is difficult to understand why EFSA doesn't start using available methods and protect European citizens. In stead they recommend more study and more dialogue.

The main focus now is on identifying common assessment groups (CAGs) for cumulative assessment. The assessment of the MOA is therefore the prime concern, though including pesticides with a common effect might be considered. In a 'refinement' pesticides can be excluded from CAGs, leading to an even more non-precautionary approach.

The opinion was used by Boobis, Ossendorp, Hamey and Moretto as a basis for a scientific article[14]. Note Ossendorp in the meantime has become chair of the EFSA PPR-panel. They are happy to conclude: "*The available data suggest that the risk from combined exposures to residues of pesticides with different modes of action is not appreciably greater than the risk from residues of the individual pesticides, when exposure is below the respective ADIs or ARfDs. In this situation, the overall risk is determined by the compound that poses the greatest risk (e.g. the highest HQ). Hence, there is no need to assess combined exposure to those pesticides with different modes of action and different target tissues, occurring as residues in foods"*. Apart from assessing pesticides in the same CAG, they propose to stop working on cumulative risk assessment.

14. Alan R. Boobis, Bernadette C. Ossendorp, Ursula Banasiak, Paul Y. Hamey, Istvan Sebestyen, Angelo Moretto, Cumulative risk assessment of pesticide residues in food, Toxicology Letters 180 (2008) 137–150.

3. OPINION ON TRIAZOLES, 2009 (PPR PANEL)[15]

Members wg. are ao. Boobis, Dewhurst, Hamey, Moretto, Van Klaveren.

Test approach of 2008-opinion on triazoles.

Seven Triazoles would be put in the CAG based on MOA and 11 based on common adverse endpoints[16] (hepatoxicity). PPR thinks they first need internationally harmonised criteria to put pesticides in a CAG!

The Hazard Index was calculated as well as RPF (relative potency factor) based on ADI and on BMD (benchmark dose), and exposure calculations deterministic and probabilistic.

15. EFSA Panel on Plant Protection Products and their Residues (PPR Panel) Scientific Opinion on risk assessment for a selected group of pesticides from the triazole group to test possible methodologies to assess cumulative effects from exposure through food from these pesticides on human health on request of EFSA. EFSA Journal 2009; 7(9):1167. [3 pp.]. doi:10.2903/j.efsa.2009.1167. Available online: www.efsa.europa.eu

16. bitertanol, cyproconazole, difenoconazole, diniconazole, epoxiconazole, flusilazole, myclobutanil, propiconazole, tebuconazole, triadimefon and triadimenol

More research is needed on probabilistic and an indication of the level of protection needed.

An 'inclusion approach' is proposed by EFSA, where pesticides will qualify for inclusion based on known MOA, and alternatively an 'exclusion approach', also including pesticides without known MOA and excluding them if (industry) presents proof they do not have a common MOA.

However there was a clear SANCO-intervention in September 2011[17] that criticizes the lack of progress of EFSA and criticizes the focus on only dose addition.

17. Cumulative Risk Assessment under Regulation (EC) 396/2005, Brussels, SANCO/E3/BD/bp D(2011)

SANCO favours inclusion & MRL-based approach/deterministic. SANCO many times heard the claim deterministic is very conservative, but never seen this quantified or compared to probabilistic.

If there is no information on a common MOA, EFSA cannot conclude there is no common MOA. Also common endpoints could count (Kortenkamp-report).

Exposure assessment: highest tier is probabilistic; SANCO agrees.

Hazard assessment: RPF based on BMD, ADIs being the lowest tier; SANCO: immediately RPF; BMD no use.

Risk characterisation: hazard index

4. EFSA OPINION ON DISSIMILAR MODE OF ACTIONS *(RESPONSE ADDITION)*

While EFSA panels for a long time tried to limit cumulative to common MOA and (very) small CAG's, at some point, probably by DG SANCO intervention, EFSA started on response addition. A report of Kortenkamp[18] states that it is of central importance to confirm in the study that there is no current example of a situation in which the concept of independent action (IA) provides an accurate prediction that is also more conservative than dose addition (DA), supporting the use of DA as a conservative default in CRA. They propose a tiered framework.

18. Investigation of the state of the science on combined actions of chemicals in food through dissimilar modes of action and proposal for science-based approach for performing related cumulative risk assessment, Andreas Kortenkamp (ULSOP), Richard Evans (ULSOP), Michael Faust (F+B), Fritz Kalberlah (FoBiG), Martin Scholze (ULSOP), Ulrike Schuhmacher-Wolz (FoBiG), European Food Safety Authority, 2012

At lower tiers, the grouping of chemicals is driven by their co-occurrence in the exposure scenarios under investigation. At higher tiers, chemicals that evoke a common adverse outcome should be grouped together.

A subsequent report of DTU, Denmark[19] mapped common CAG's for responses. An additional report of RIVM/ANSES/IPCS on neurotoxicity, reprotoxicity and liver toxicity was produced in January 2013. In total 257 substances were found to have reproductive and developmental toxicity, 67 substances were found to be neurotoxic, and 244 substances to cause effects on the liver and biliary system, including the gallbladder. The report advises to look at the MoA and decide with expert judgement on CAG's.

19. Identification of Cumulative Assessment Groups of Pesticides, Dr. Elsa Nielsen, Dr. Pia Nørhede, Dr. Julie Boberg, Dr. Louise Krag Isling, Dr. Stine Kroghsbo, Dr. Niels Hadrup, Dr. Lea Bredsdorff, Dr. Alicja Mortensen, Dr. John Christian Larsen, National Food Institute, Technical University of Denmark, EFSA 2012.

I.5. CUMULATIVE EFFECTS AS STUDIED IN NON-PESTICIDE AREAS

CHEMICALS IN GENERAL

REACH doesn't offer much on mixtures, but Council did:

In the Council conclusions from 22nd December 2009, the Commission was invited, drawing on existing and future research and paying appropriate attention to the costs and benefits, to assess how and whether relevant existing Community legislation adequately addresses risks from exposure to multiple chemicals from different sources and pathways, and on this basis to consider appropriate modifications, guidelines and assessment methods, and report back to the Council by early 2012 at the latest.

Andreas Kortenkamp made a state-of-the-art document for DG Env. on mixtures[20] which is heavily attacked by industry. Kortenkamp first of all states there are effects of a mixture of

20. State of the Art Report on Mixture Toxicity, Prof. Dr. Andreas Kortenkamp (ULSOP), Assoc.-Prof. Dr. Thomas Backhaus (UGOT), Dr. Michael Faust (FBEC), 2009

chemicals at their NOAEL ('something from nothing'). Later SCHER (SANCO SCHER Committee published an opinion on mixture toxicity[21] in 2011, prepared by a working group[22].) disagreed and claimed there is a no-effect level somewhere below NOAEL.

Kortenkamp also claims joint effects of mixtures of dissimilar acting chemicals. Industry and SCHER committee attacked this saying the articles Kortenkamp put forward as a basis for his conclusions were 'over-interpreted", so they keep on claiming chemicals with a different mode of action have no cumulative effects, but independent action (IA).

Next point is Kortenkamp saying the uncertainty factors used (in humans, 2x 10) are not sufficient to include mixture toxicity. This again is attacked by SCHER saying if you have 1/100 of NOAEL joint effects won't happen.

Kortenkamp says synergy is quite rare and SCHER is saying it happens only in a few cases at high doses (based on an ILSI/ Boobis article).

SCHER, like EFSA, likes to focus on well-known situations (MoA known, level known) and do the dose-addition.

SCHER however in its recent draft for consultation finally proposed to use dose addition (DA) for known mixtures with unknown MoA to be on the conservative site. But for the unknown mixtures -the large majority of the cases- they propose nothing, no RA possible (except in the case the whole mixture is tested).

They also propose for the few 'known' mixtures to do a tiered approach. First they look if the exposure is 'significant'. Next as a lower tier they use TTC (based on Boobis-article), so many possibilities for stopping the assessment at a low point. Then the DA and next allowing all kinds of calculations and assumptions as in traditional RA.

21. Toxicity and Assessment of Chemical Mixtures, Scientific Committee on Consumer Safety (SCCS), Scientific Committee on Health and Environmental Risks (SCHER), Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), May/June 2011

22. Herman AUTRUP, Jim BRIDGES, Arielle GARD FLOC'H, Helmut GREIM (chair), Ari HIRVONEN, Colin JANSSEN, Christophe ROUSSELLE, Tore SANNER, Jose TARAZONA, Emanuela TESTAI, Theo VERMEIRE, Marco VIGHI, External Experts: Alan BOOBIS. Claudia FRUIJTIER-PÖLLOTH (rapporteur)

layout and design: Krisztina Mogyoró k.mogyoro@envitrend.hu