EFSA

SCIENCE OR IDEOLOGY?

EFSA'S HAPPY GENOTOX MARRIAGE WITH INDUSTRY-FUNDED ILSI.

PAN Europe
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SUMMARY

SCIENCE OR IDEOLOGY.

In a survey about EFSA's scientific opinions on genotoxicity, PAN Europe found out that Food Authority EFSA's conclusions systematically end up at the side of (free market) ideology of lowering costs for industry and of helping get pesticides on the market. In a spectrum ranging from a more scientific (i.e. objective approach and more human protective) policy (left) to ultimately a more ideological position (right) that lowers the bar for human health and eases the approval of pesticides, EFSA figures in the two right boxes (see image below). Regarding the most toxic class of chemicals, genotoxic pesticides (DNA-reactive chemicals), EFSA shows that commercial interests are considered as more important than following its mission to protect the public.

MORE SCIENTIFIC		MORE IDEOLOGIC	
Experimental results as a basis for decisions, using current scientific insights	Traditional Risk assessment; based on experimental results (submitted by industry) and on assumptions (expert judgement)	Extending traditional risk assessment with new elements that lowers human protection and ease approval of pesticides	Deviating from EU policy/law that lowers human protection and ease approval of pesticides
0 EFSA opinion	0 EFSA opinion	4 EFSA opinions	5 EFSA opinions

In none of the nine cases studied EFSA is following current scientific insights (most left in the spectrum) as required by the pesticide Regulation, while in no case studied even traditional risk assessment is followed. The two boxes on the right side, which favour commercial interests over human health (and are part of the free market ideology), are the ones that categorise EFSA's opinions in this survey on genotoxins. Ideology over science. That is PAN Europe's conclusion, analysing nine EFSA working groups and regulatory meetings regarding the most toxic pesticides on the market, genotoxins (DNA-reactive) pesticides (8 cases) and endocrine disruptors (1 case) over the past 15 years. In stead of protection EU citizens against the harms of genotoxins, as the EU Food Law provides for, EFSA does the opposite and allows citizens to be exposed to these harmful genotoxins. Even after 2009 when the EU decided that any contact between humans and genotoxic pesticides (as well as from endocrine disrupting pesticides) should be excluded, EFSA kept on adopting opinions in contradiction with these rules. We demonstrate in this report that EFSA designed loopholes to find a way to classify these dangerous chemicals (genotoxic pesticide metabolites, genotoxic pesticide impurities and genotoxic mixtures) as safe.

IS IT EFSA'S MISSION TO HELP COMMERCE?

Already in 2005, just after EFSA's debut in the field, in a meeting co-organised with industry-funded group ILSI[1], EFSA concluded that a safe level could be derived for genotoxins (even for genotoxic carcinogens) in case of 'unavoidable' contamination. Additional 'red lines' were crossed, even after 2009, by adopting two different tools (MOE, margin of exposure; TTC, threshold of toxicological concern) that did allow contact with humans, in contrast with EU policy. The tools were designed and promoted by industry advocacy groups and many of the experts at the drawing board made its way into EFSA working groups. Remarkably, the opinions on MOE (2012) and TTC (2014) were an own initiative of EFSA, and not mandated from the Commission, suggesting that EFSA itself is part of a pressure group. Genotoxic pesticide impurities were considered by EFSA as a "big problem" because more and more genotoxins were discovered with sensitive assays. EFSA's approach was not to ban the genotoxins and protect the public, but to find a way to grant market access. It was thus not so much a human health "problem" that EFSA identified, but a commercial problem.

EU POLICY ON GENOTOXICITY DISMANTLED STEP BY STEP

In the 2005-opinions the lifted restrictions on genotoxins (safe thresholds for genotoxins) were claimed to be only for cases of "unavoidable" contamination. Step by step EFSA changed its position, first allowing genotoxic pesticide metabolites and in a later phase genotoxic pesticide impurities in food. Both types of contamination could be avoided by not approving the pesticides. People are now exposed to harmful pesticide metabolites like Hydrazine (classified as a proven carcinogen 1B) and Anilin (classified as M2 C2, suspected mutagen and carcinogen) due to this EFSA policy.

Restrictions for testing were also lifted (2011). The most protective test for the public (in-vivo) was dropped by EFSA for animal welfare reasons, demonstrating that EFSA favours animal welfare interests over human health.

For genotoxic mixtures (2018) numerous escapes from being considered unsafe are presented by EFSA for genotoxins (low doses are safe, genotoxicity could be a 'secondary' effect, MOE, TTC applied, etc.). Genotoxins thus can achieve the 'safe' verdict. EFSA in fact takes political decisions that are not in its remit.

EFSA's continued claim of a safe threshold are contradicted by independent literature. Scientists consider a threshold for genotoxins unlikely and claim that there is no experimental proof for a safe threshold. These studies, however, were not considered by EFSA in its opinions.

EFSA'S LOVE FOR ILSI

From its beginnings, EFSA is known for having very close relations with industry and industry-funded groups like ILSI and was forced in 2014 by the European parliament to adopt a conflict of interest policy. We show in this report that in the field of genotoxicity we surveyed, nothing has changed. The same experts are still part of the working groups with a past or present relations with ILSI or other advocacy groups, also after 2014. Sometimes (2018) even industry consultants are included in working groups. Recently, the EFSA 2018-working group on genotoxic mixtures and the EFSA 2019-guideline on TTC feature a majority of experts with familiar names and a questionable independence, just as the previous working groups before 2014. And still, at the same time, a minority of the experts are active scientists. This also raises the question who selected these experts. We still don't know. EFSA refuses to hand over documents on the selection procedures for each of the 5 'access to documents' requests PAN Europe carried out in 2020. EFSA's rules oblige documentation, but this is either not implemented by EFSA or kept hidden from the public. What we do know is that a big majority of EFSA management (11 out of 13 we assessed) either comes from industry (lobby groups) or has questionable relations with industry funded groups or attends industry-funded meetings.

EFSA has a very remarkable relation to ILSI, the industry-funded group that promotes risk assessment ideas for easing chemical market access[2]. Not only are EFSA's working groups crowded with experts that have links to ILSI, and EFSA staff has employees that came through the revolving door, EFSA also convenes partnership meeting with ILSI. One of these meetings was on TTC in 2011 *"to overcome hurdles to acceptance of TTC"*, and creates the impression that EFSA is part of an advocacy group to get a risk assessment tool adopted against resistance from the outside world. The close relation with ILSI has been criticized much by civil society and the European Parliament, but remains in place nonetheless.

ENDOCRINE DISRUPTION, THE SAME STORY

In the related field of endocrine disruption, also part of the most toxic pesticide groups (and subject to the 'hazard approach' that bans contacts to humans as well), the same conclusion can be drawn as on genotoxins. Science as published by the many thousands of academic endocrinologists is disregarded. The recent letter by the Endocrine Society[3] tells the story: work done by world top-level endocrinologists (this time on non-monotonic dose-response curves) is ignored by EFSA.

EFSA'S REMAKE NEEDED URGENTLY

PAN Europe concludes that a full remake of EFSA is needed. More independent people are needed in the EFSA management, more independent experts in the working groups and regulatory experts and civil servants substituted by active scientists. And experts with a questionable independence removed from the selection lists for working groups and panels. Also many of the opinions than have been designed by its working groups should be revised, to start with the ones on genotoxicity and endocrine disruption. Own mandate opinions of EFSA should be ended and mandates designed only in an open democratic way.

1. INTRODUCTION

In 2008, the European Union adopted a new policy, the so-called 'hazard approach', in pesticide Regulation 1107/2009 for a group of extremely dangerous pesticides. If pesticides are classified as carcinogenic, mutagenic or reprotoxic (class 1) or considered endocrine disrupting or persistent and bio accumulative, they are part of this 'hazard approach' and will in principle be banned. EU politicians decided to adopt this approach after numerous scientific studies showed that it cannot be proven experimentally that even low doses of these substances are safe and that they cannot be contained once released in the environment. The unanimous decision of 27 EU Member States, Commission and EU Parliament therefore was to rule that EU citizens shall not be exposed to these chemicals ("no contact with humans", according to Annex II of the Regulation).

Despite this provision in law several interest groups like industry kept on challenging these rules as well as many importing countries (eg. USA, Brazil). Even several Commission services favoured trade interests over protecting public health, and helped attacking the law[4]. In drafting an opinion on the criteria for endocrine disrupting pesticides, EU Food Authority EFSA clearly has chosen side with commercial interest groups and other lobby groups that opposed the new policy. This experience triggered this investigation to better understand if EFSA's opinion on endocrine disruption is representative for the attitude of EFSA on the new 'hazard' policy, and to find out if it is just one incident or part of a pattern. EFSA is put in place to present scientific opinions based on current scientific knowledge and with this research PAN Europe will try to find out if EFSA attacks the new policy in general as well as we like to analyse EFSA's attitude towards independent science as published by academic scientists. Are EFSA's opinions based on current (peer-reviewed) science or are they based on other grounds such as non-peer-reviewed studies or non-data-based views like expert judgement or even part of a specific thought school.

2.
RESEARCH QUESTIONS

How do EFSA opinions on hazard pesticides/substances relate to academic science as published in peer-reviewed journals?

How do EFSA opinions on hazard pesticides/substances relate to non-peer-reviewed studies, in particular those published by industry?

What is the role of non-experimental based views and feelings in EFSA's opinions, such as 'expert judgement' and 'weight of the evidence'?

Is EFSA opposing to EU's hazard approach in general? Is EFSA acting in a pure scientific way or does ideology play its part?

What is the background of the experts that EFSA selects for drafting opinions on hazardous properties of pesticides; are they part of specific thought schools ?

How do these selections relate to EFSA's policy on selecting experts and what is its practice?

What is the background of EFSA's management (those selecting experts)?

The questions will be answered by selecting case studies that are related to the hazard approach, mainly to opinions and working groups on genotoxicity and opinions that aim at setting "safe levels" for genotoxic substances such as TTC. The case on endocrine disruption will be added for comparison reasons. The opinions will be benchmarked with independent peer-reviewed academic studies.

3.
SELECTION OF CASE STUDIES

EFSA on genotoxic carcinogens 2005
EFSA/ILSI co-meeting 2005
EFSA genotoxicity testing, 2011
EFSA TTC for carcinogens, 2010 – 2012
EFSA MOE for carcinogens, 2012
EFSA/ILSI co-meeting on TTC, 2011
EFSA review for TTC, 2014
EFSA genotoxicity standing group, 2015 – 2018
EFSA genotoxicity testing of mixtures, 2018
EFSA TTC Guidance TTC 2019
EFSA, criteria for endocrine disruption, 2013

4. METHODOLOGY

PAN started by sending "access to documents" requests to EFSA on selected EFSA working groups that have been composed to write an opinion on genotoxicity. We asked for all documents on the mandate, the selection of the chair and the experts, the meeting documents and internal discussions. We also analysed the data we could find on the internet regarding the background of the chosen experts and their relations to lobby groups or specific ideologies.

On science we did a survey on PubMed and analysed reviews of independent scientists on the topics of the working group, on genotoxicity, the relevance of thresholds, etc. These independent views were compared to the views of the EFSA working groups.

On science we especially tried to find out how EFSA is positioned between to different (and many times competing) views. One position are the views expressed by academic scientists in peer-reviewed articles in scientific journals. Scientists are also humans with a certain bias, but there is generally no (commercial) interest that will cause bias. The position from academia therefore is considered here as open and neutral. Ideology is also something that plays a role. We will put the scientific position against an extreme ideological (but in policy dominant) position of what we will call the "free market ideology", the view that it is important, in order to be globally competitive, to lower the costs for industry, for instance by limiting safety testing or adopting cheap (non-animal) testing options, the view that there is overregulation and rules need to be reduced and it should be 'left to the market' to take responsibility, and the -often connected- view or belief that low doses of chemicals are safe and that 'safe levels' always do exist. It also mostly includes being sensitive on direct costs for industry or farmers, but -at the same time- ignoring the generally big external costs due to the harms done by chemicals (health care, human suffering, biodiversity decline, pollution of the planet) or assuming external costs do not exist.

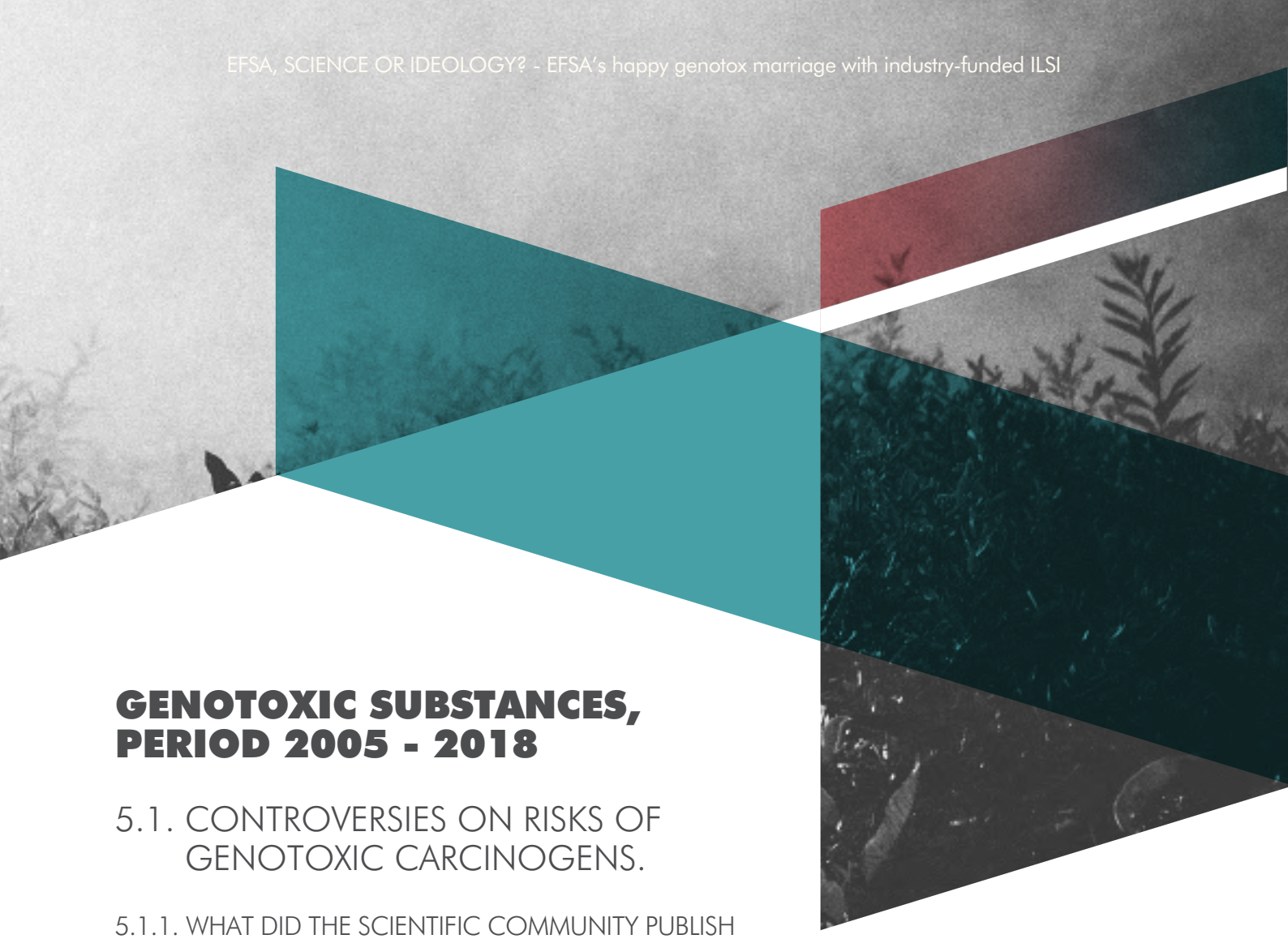
We will analyse the different working groups to position EFSA somewhere between the opposing (dominant) views.

5. RESULTS

EFSA took around 9 months in total (2x15 days is the legal period) to respond to all access to document requests. EFSA several times claimed that documents could not be recovered (not in the system anymore) or in many cases claimed that there are no documents, even if the internal rules (SOP, Standard Operation Procedures[5]) require recordings. The continued EFSA claims on being transparent (*"we should highlight that EFSA, due to its maximum commitment to the core values of transparency and independence, continually endeavours to further increase its engagement with civil society"*) could not be confirmed by PAN Europe in this survey. It takes months to obtain an answer and even then only a partial picture emerges. We can also not control if documents are withheld or not 'found'. For instance, the SOP requires that the chair of an EFSA panel makes a proposal for a chair of a new working group and has a discussion with EFSA's Head of Unit on the composition of a new working group, including lists of required expertise, etc. But this 'discussion' is not documented, and no one can find out what happens behind the screens of EFSA.

For a citizen it is close to impossible to have an idea whether EFSA follows its own internal rules or not.

Below you will find an assessment of the different working groups and meetings selected and assessed by PAN Europe. We analysed the composition and the background of the selected experts. It is well-known that many experts in EFSA working groups and panels have conflicts of interests, in 2013 in the publication of journalist S. Horel (Unhappy meal[6]), more than half of the experts are claimed to have a conflict of interest. This percentage was still 46% in 2017[7]. All in clear violation of the EU Food Law 178/2002[8] that put EFSA in place and requires an independent assessment[9]. We also analysed for each topic what independent scientists conclude and what these working groups conclude. We have started the work with the working group on endocrine disruption that alarmed us of the fact that EFSA was undermining EU law and the 'hazard' approach and will proceed with groups working on genotoxicity and end with groups that design a safe level for genotoxic chemicals.



GENOTOXIC SUBSTANCES, PERIOD 2005 - 2018

5.1. CONTROVERSIES ON RISKS OF GENOTOXIC CARCINOGENS.

5.1.1. WHAT DID THE SCIENTIFIC COMMUNITY PUBLISH ON THE RISKS OF GENOTOXIC SUBSTANCES AND THRESHOLDS?

The discussion here is mainly around the existence of safe levels (thresholds) for genotoxic substances. But the discussion could be extended to non-genotoxic substances? Do safe levels exist in general? And for what type of chemicals? Calabrese et al.[10], using a database of 2189 chemicals and 56914 studies (yeast screening), reject the long-held assumption in toxicology that there is a threshold dose below which no adverse effects will be seen. His data call for the rejection of the monotonic dose-response threshold model for low-dose prediction, and they support the hormetic model as the default model for scientific interpretation of low-dose toxicological responses.

Sheehan[11] concluded the same for oestrogenic compounds. His findings contradict the threshold assumption and low-dose safety. No thresholds were observed. Calculating risk and assuming additivity of effects from multiple chemicals acting through the same mechanism rather than assuming a safe dose for non-threshold curves is appropriate, he concludes. Slob[12] comes to the same conclusion: The main lesson from his analysis is that there is no evidence whatsoever for a dose-threshold. A non-threshold dose-response curve is perfectly in agree-

ment with the data. Beronius et al.[13] note that the general argument for assuming no threshold for endocrine disrupting chemicals was that compounds that act by the same mechanism as endogenous factors, e.g. hormones, just add to the actions of these factors and increase the response of already ongoing biological processes. This "additivity-to background" argument has also been made to defend a no-threshold-approach for genotoxic carcinogens and that thresholds in risk assessment are more connected to adverse effects. Conolly and Lutz (2004[14]) state that the first interaction of a toxic agent with its primary biological target molecule is likely to have no threshold but imply that the complexity of a biological system makes non-threshold dose-response curves unlikely for many "higher" endpoints, such as behaviour, reproduction, organ weights and growth.

Apart from the 'threshold' discussion, low dose effects are also a neglected area in toxicology. Lanphear[15], argues for zero exposure for many chemicals. He concludes: *"If widely disseminated chemicals and pollutants like radon, lead, airborne particles, asbestos, tobacco, and benzene do not exhibit a threshold and are proportionately more toxic at the lowest levels of exposure, we will need to achieve near-zero exposures to protect public health"*.

The WHO-UNEP report on endocrine disrupting chemicals[16] criticises the low-dose safety assumptions for this type of chemicals: *"The doses declared safe are not actually tested, nor are the mixtures. These studies also assume that there is a threshold for EDC effects, that there will be no effects at low doses and that the dose–response curve rises with increasing dose. There is no threshold for EDC effects due to the presence of active hormone pathways, and EDCs are likely to have effects at low doses. Consequently, their dose–response curves will not necessarily rise in proportion to dose"*. The report points out that timing of exposures is also critical, as exposures during development likely lead to irreversible effects, whereas the effects of adult exposures seem to go away when the EDC is removed. Sensitivity to endocrine disruption is highest during tissue development.

For genotoxic substances, thresholds are generally not assumed. Slob[17] refers to a basic argument underlying this assumption that a single or just a few molecules cannot be sufficient to engender significant changes in whole organisms, with resulting health effects. And genotoxic carcinogens are generally considered as an exception to this, because theoretically a single molecule might irreversibly damage DNA in a way that can increase a single cell's probability to turn into a malignant cell. The notion that agents causing non-cancer effects must have a dose-threshold is substantiated by typical biological phenomena as homeostasis and repair. The latter is sometimes used as an argument to believe that even genotoxic agents must have thresholds, because the DNA repair system should easily be able to handle small increases in DNA damage. Slob mentions a famous example, the RfD (reference dose, or human exposure limit) for dioxin (2,3,5,6-TCDD) turns out very differently when based on the linearized multistage model (no threshold assumed) or when based on the no observable adverse effect level (NOAEL) approach (threshold assumed), even when the same experimental data are used. This illustrates that the threshold discussion is also of practical importance. He argues that the existence of dose-thresholds in a strict quantitative sense, and the associated approach of analysing dose-response data, is hard to defend. Already only because of the limitations of analysis sensitivity.

Current insights in science should also be taken into account. Carcinogenic effects could not only be the result of DNA-active chemicals, but also from low doses of chemicals causing genome instability by interfering with DNA repair, epigenetic modification and pathways, DNA damage signalling, telomere length, mitochondrial function[18].

WHAT DO 'FREE MARKET' INTEREST GROUPS CONCLUDE?

Industry advocacy group ILSI Europe in 2016[19] put it this way: *"It is recognised that current risk analysis approaches to compounds in food that are genotoxic and carcinogenic in experimental animals may sometimes incur disproportionate or even unnecessary measures on the part of regulators and industry"*. This already demonstrates that ILSI's mission is more about 'unnecessary measures" than about science. And: *"The current ILSI Europe expert group was convened in 2002 with the following objectives: (1) to propose a structured approach for the evaluation of genotoxic carcinogens in food following a critical review of the approaches currently available; and (2) to evaluate the margin of exposure approach for food-borne substances that are genotoxic and carcinogenic"*. They claim that 'historically', DNA-reactive carcinogens have no threshold but that threshold exists in the dose–response relationship for compounds that produce cancers via a non-DNA-reactive mechanism. Further, they consider a range of elements (non-relevance of the tumours for humans, is the mechanism of action known, repair mechanisms, etc.) in an attempt to limit the (non-threshold) cases of DNA-reactive carcinogens. And ultimately the main proposal for genotoxic carcinogens is to use MOE (Margin of Exposure): *"Overall, the MOE is the most appropriate default approach because it combines information on potency and exposure, without the generation of numerical risk estimates of unknown reliability. Both the T25 and BMD approaches could be used as reference points on the intake response relationship to calculate MOEs for the comparison of the foodborne carcinogens selected"* and TTC (Threshold of Toxicological Concern): *"to apply the TTC concept to extremely low exposures using data from cancer bioassays on chemicals in the same structural class. Although there is a general consensus that it is not possible to define an intake for a DNA-reactive carcinogen that would give a zero risk, the threshold of toxicological concern (TTC) concept provides a practical and conservative approach that could be used to formulate advice to risk managers when exposures are very low (Kroes et al., 2004[20])"*. Thus, a threshold is recommended, except in a few limited cases.

EFSA'S WORK, OPINION ON GENOTOXIC CARCINOGENS, 2005.

EFSA assumes that there is a consensus that genotoxic carcinogens should not be deliberately added to food. And that no contact to humans (no safe level) should be the policy followed. But EFSA opens the door for 'unavoidable contaminants and natural toxicants'. In that case a threshold can be applied, based on MOE, the margin of exposure. EFSA Scientific Committee considered that an MOE of 10,000 or more, based on animal cancer bioassay data, ''would be of low concern from a public health point of view and might reasonably be considered as a low priority for risk management actions'' (EFSA, 2005[21]). EFSA feels that an MOE of 10,000 and above, based on a BMDL10 from an animal study, would be a value that would indicate a low concern from a public health point of view and that might be considered a low priority for risk management actions. The rationale for this value was twofold. A 100-fold difference between the BMDL and human exposure would be necessary to take into account general issues of species differences and human variability (analogous to the use of a 100-fold uncertainty factor for threshold toxicants). A further 100-fold difference would be necessary because of additional uncertainties related to human variability in cell cycle control and DNA repair, and because the shape of the dose–response curve below the BMD and the dose level below which the cancer incidence is not increased are unknown.

The EFSA wg. completely disregards effects from low doses of chemicals causing genome instability by interfering with DNA repair, epigenetic modification and pathways, DNA damage signalling, telomere length and mitochondrial function[22]. They only discuss effects acknowledged many decades ago.

The EFSA working group that drafted its position is given below (Table 1). At that time (2005) EFSA failed to have a conflict of interest policy and seemed to have close ties to experts that are linked to -especially- industry advocacy group ILSI.

TABLE 1. COMPOSITION EFSA'S WORKING GROUP ON THE 2005 OPINION ON GENOTOXIC CARCINOGENS.

NAME & TITLE	INSTITUTE	TYPE OF EXPERT	INDEPENDENCE[23]
A Knaap (chair)	National Institute of Public Health and the Environment (RIVM	Civil servant	ILSI, Unilever
C.Anderson	No information available		
P. Branton			consultant
J. Bridges	University of Surrey	retired scientist	ILSI board member
T. Crebelli	Istituto Superiore di Sanità, Rome, Italy	scientist	IWTG wg. (industry chaired), publications with industry
H. Greim	Technical University of Munich	Retired	industry consultant
JC. Larsen	Danish Institute for Food and Veterinary Research	Civil servant	ILSI (scientific advisory committee)
D. McGregor	No information		
A Renwick	University of Southampton	scientist	ILSI task force
J. Schlatter	Swiss Federal Office of Public Health	Civil servant	ILSI board of trustees and long range of ILSI committees

Conclusion on composition of the wg.:

8 out of 10 experts have a questionable independence, while EU Food Law[24] provide for "independent scientists" to be included in working groups;

only few are active scientist

5.2 MEETING ON GENOTOXIC CARCINOGENS (EFSA-ILSI PARTNERSHIP), 2005.

This meeting was a very strange one since it was organised by an industry funded group (ILSI) together with EFSA. An invited-only meeting thus of industry and civil servants, excluding other stakeholders. Why would EFSA meet with one stakeholder, excluding others? This raised questions about EFSA's objectivity and independence. One basis for the discussion was: *"ILSI Europe Expert Group draft paper on Approaches to the Risk Assessment of Genotoxic Carcinogens in Food: A Critical Appraisal (submitted for publication: O'Brien et al., 2006)"* with: Renwick, Schlatter, Dybing, Benford, Edler, Van Benthem.

Among the about 120 attendants, half were industry employee or linked to industry funded groups such as ILSI (International Life Sciences Institute), but generally not openly mentioning this connection, and the other half were (national) civil servants, see a range of examples in the graph below. Several experts took the opportunity to write an article on the (claimed) outcome of the meeting[25].

TABLE 2. EFSA-ILSI PARTNERSHIP, 2005 INVITED-ONLY MEETING.

NAME	INSTITUTE	TYPE OF EXPERT	INDEPENDENCE
S.Barlow	-	consultant	ILSI, published with industry employees
JC Larsen	Danish Institute for Food and Veterinary Research	Civil servant	ILSI (industry lobby group)
D. Benford	Food Standards Agency UK	civil servant	2000 Author of ILSI monograph on acceptable daily intake; 2001 Author ILSI monograph risk assessment of food; 2008 ILSI workshop MOE (Rhodes); 2009 -2012 member ILSI Europe wg on benchmark dose (BMD); 2006- 2010 member ILSI Europe wg on margin of exposure (MOE); 2010 Author ILSI publication MOE, Food and Chemical Toxicology 48 (2010) S2–S24; 2014 meeting ILSI-HESI workshop on Genetic Toxicology
JW Bridges	University of Surrey	retired scientist	ILSI board member
E Dybing	Norwegian Institute of Public Health		ILSI expert group
L. Edler	German Cancer Research Center (DKFZ)		Several ILSI working groups
S. Felter	Procter & Gamble	Industry expert	Industry employee
CL Galli	University of Milan	Scientist / industry consultant	Member ILSI TTC taskforce 2013 – 2016; Partner ILSI research program FOSIE 2002; publication with ILSI on TTC in 2000 and 2007; member scientific advice committee CEFIC 2013 – 2016; member Board of Directors ILSI Brussels 2013 – 2016;
J Kleiner	ILSI, now EFSA	Regulatory expert	Employee ILSI, now EFSA
B Bottex	ILSI, now EFSA	Regulatory expert	Employee ILSI, now EFSA
A Knaap	National Institute of Public Health and the Environment (RIVM	Civil servant	ILSI, Unilever
R. Kroes	Utrecht University – IRAS	Retired scientist	ILSI
SS Olin	ILSI Risk Science Institute	Regulatory expert	ILSI employee
AG Renwick	University of Southampton	scientist	ILSI task force
J Schlatter	Swiss Federal Office of Public Health	Civil servant	ILSI board of trustees and long range of ILSI committees
J Van Benthum	National Institute of Public Health and the Environment (RIVM)	Civil servant	ILSI, member working group and committees
HA Greim	Technical University of Munich	Retired	industry consultancies
Many other industry employees	Unilever, Nestle, Coca-Cola, Danone, PepsiCo, DSM, Procter %Gamble, etc.		

Summary:

About half of the attendants were industry employees or industry funded groups such as ILSI;

NGO's were not invited

A clear violation of the EU Food Law 178/2002 on independence

The EFSA opinion, that was published after the meeting, was, weirdly enough very similar to the outcome of this meeting and the article of Barlow et al.[26] that tried to put MOE in the saddle was very enlightening on how EFSA embraced the theories of the industry: *"The conference concluded that the MOE approach was a useful and pragmatic option for risk assessment of substances that are both genotoxic and carcinogenic. It has the potential to improve the advice provided to risk managers, since it allows comparison between compounds and prioritisation of risk management actions, especially if the MOE is accompanied by an appropriate narrative explaining inherent uncertainties"*. It is especially applied on genotoxic pesticide metabolites i. This is contradicting the principle from 2005 that it should be only about non-intentional exposure of humans, while metabolites are clearly intentional exposure. For instance, the pesticide Buprofezin was considered as acceptable by EFSA, while operators and residents could be exposed to the mutagenic and carcinogenic metabolite anilin (M2, C2). For Maleic hydrazide, the same happened: the classified metabolite Hydrazine is a classified carcinogen (C1B) approved on the market (see Table 4 for more details). On top of this, the industry goes to big lengths to classify metabolites as "non relevant" (based on a few in vitro studies) which clears the way for approval.

5.3. EFSA OPINION ON GENOTOXICITY TESTING, 2011 (OWN INITIATIVE).

The pesticide data requirements regulation 283/2013 provides for: *"If all the results of the in vitro studies are negative, at least one in vivo study shall be done with demonstration of exposure to the test tissue (such as cell toxicity or toxicokinetic data), unless valid in vivo micronucleus data are generated within a repeat dose study and the in vivo micronucleus test is the appropriate test to be conducted to address this information requirement"*. And: *"In vivo studies in germ cells: The necessity for conducting these tests shall be considered on a case-by-case basis, taking into account information regarding toxicokinetics, use and anticipated exposure"*.

EFSA's 2011[27] opinion however concludes: *"In the event of negative in vitro results, it can be concluded that the substance has no genotoxic potential. In case of inconclusive, contradictory or equivocal results, it may be appropriate to conduct further testing in vitro. In case of positive in vitro results, review of the available relevant data on the test substance and, where necessary, an appropriate in vivo study to assess whether the genotoxic potential observed in vitro is expressed in vivo is recommended"*. And advises the following approach: *"The Scientific Committee recommends a step-wise approach for the generation and evaluation of data on genotoxic potential, comprising: - a basic battery of in vitro tests, - consideration of whether specific features of the test substance might require substitution of one or more of the recommended in vitro tests by other in vitro or in vivo tests in the basic battery, - in the event of positive results from the basic battery, review of all the available relevant data on the test substance, and - where necessary, conduct of an appropriate in vivo study (or studies) to assess whether the genotoxic potential observed in vitro is expressed in vivo"*.

An expensive in-vivo test was kept out, *"The Scientific Committee did consider whether an in vivo test should be included in the first step of testing and broadly agreed that it should not be routinely included"*. Adding: *"However, if there are indications for the substance of interest that specific metabolic pathways would be lacking in the standard in vitro systems, or it is known that the in vitro test system is inappropriate for that substance or for its mode of action, testing may require either appropriate modification of the in vitro tests or use of an in vivo test at an early stage of testing"*.

Regarding testing germ cells, EFSA concludes: *"The Scientific Committee concluded that routine testing for genotoxicity in germ cells is not necessary"*.

As a further clarification of its advice, EFSA states that testing needs to be weighed against: "the need to ensure that such tests do not generate a high number of false positive results, because that has undesirable implications for animal welfare, e.g. by triggering unnecessary in vivo studies". The EFSA here clearly advocates to reduce human health protection. 'False positive' is the main argument of the working group for dropping test requirements, even tests required in REACH: *"In the REACH guidance, the mouse lymphoma has been introduced for cases in which both Ames and MNvit are negative, but it is well known that increasing the number of tests increases the likelihood of false positive results . The suggestion of the WG would be not to perform another test but to leave flexibility to expert judgement (on a case-by-case basis)"*.

The working group is also arguing for the reduction of 3 to 2 *in vitro* tests. The underlying data for this position is a study by the Flavour industry, done by Kirkland and colleagues in the UK. There is little doubt that the 'hearing expert' Kirkland and the network he maintains[28] plays an important role in this EFSA opinion. It is strange to note that civil servants from JRC (Corvi, Marzin) and EFSA (Maurici) are part of these networks that claim to be active on reducing false positives. Other networks operate in this area, such as EEMS[29], heavily sponsored by industry and co-operating with industry research group ECETOC, with much of the same people and Kirkland as a President for some time. Another (overlapping) initiative comes from the EU Joint Research Centre (JRC) to reduce animal testing for genotoxicity testing[30] (ECVAM), inviting experts with heavy conflicts of interest (Barlow, Kirkland).

In conclusion, EFSA proposes weaker testing for genotoxicity, no standard in vivo test of somatic cells and no studies in germ cells. The self-mandate was justified by referring to discussions in ILSI-HESI groups (IVGT[31]) and another initiative, the 'International Working Group on Genotoxicity Testing' (IWTG) promoting alternatives for in vivo testing (the 5 references in the mandate are all industry studies).

The self-mandate looks like a hardly covered industry attempt to lower the bar for genotoxicity testing, claiming they deeply care about avoiding animal testing (why not care about human exposure?) and avoiding false positives (why worry about false positives and not care about false negatives?). Weirdly enough, the topic of a threshold was discussed again, and promoted[32] while "threshold solutions" were discussed (MOE, TTC) that have little relevance to testing.

A déja-vu

TABLE 3. COMPOSITION OF THE EFSA WORKING GROUP DRAFTING THE 2011 GENOTOXICITY TEST OPINION.

NAME & TITLE	INSTITUTE	TYPE OF EXPERT	INDEPENDENCE
S. Barlow (chair)	-	consultant	Work for ILSI and (cigarette) industry
G. Aquilina	Istituto Superiore Sanità	scientist	
ML. Binderup	COWI – Dept Health	Civil servant Denmark	
C. Bolognesi	Istituto Ricerca sul Cancro	scientist	
P. Brantom	-	consultant	
R. Corvi	ECVAM – DG JRC	Civil servant - Commission	ECVAM
R. Crebelli	Istituto Superiore Sanità	scientist	IWTG group, publication with industry; ILSI activity of food packaging
E. Dogliotti	Istituto Superiore Sanità	scientist	
M. Filipic	National Institute of Biology	Civil servant - Slovenia	
C. Galli	Uni Milano	scientist	ILSI, board of directors, task force, CEFIC, COLIPA
R. Guertier	BfR	Civil servant - Germany	
A Hartwig	Uni Berlin	Scientist - Germany	
P. Kasper	BfArM (Federal Institute for Drugs and Medical Devices), Bonn	Civil servant - Germany	ECVAM, EEMS
D. Kirkland	Covance Laboratories Ltd., Otley Road, Harrogate HG3 1PY, UK; Kirkland consulting	Consultant/hearing expert	Industry consultant, ILSI, EEMS, ECVAM
D. Lovell	Uni of London		IWTG group (industry-chaired), publication with industry ; industry consultant, worked for Pfizer
D. Marzin	Pasteur Institute/ ECVAM		IWTG group, publication with industry, ECVAM
J. van Benthem	RIVM	Civil servant - Netherlands	ILSI IVTG-wg, co-chair ILSI Genetic Toxicology Technical Committee; ECVAM

Conclusion on the composition of the wg.:

Again several experts are linked to ILSI, that has been actively promoting a specific outcome on genotoxicity testing

Few independent scientists have been selected by EFSA

EFSA favours 'animal welfare' over 'human health' by opposing in-vivo testing for genotoxicity

EFSA cares a lot about the possibility of 'false positives' while no attention is paid for 'false negatives', and -again- favours market access of chemicals over protecting human

Genotoxicity testing is also included in the 2003 SANTE Guideline on the relevance of metabolites[33]. The Guideline provides for: "All metabolites that have passed step 1, step 2 and stage 1 of step 3 should be screened for their genotoxic activity by at least the following package of in vitro genotoxicity studies: Ames test, gene mutation test with mammalian cells, and chromosome aberration test. Equivocal results in in vitro studies should be substantiated by in vivo experiments. Mutagenic metabolites (any category) are considered relevant". EFSA's 2011-opinion reduces this to two tests: - a bacterial reverse mutation test (OECD TG 471, Ames-test), and - an in vitro mammalian cell micronucleus test (OECD TG 487). This all translates in EFSA's risk assessment practice to allow humans being exposed to carcinogenic metabolites. In Table 4 below you will find examples of genotoxic pesticide metabolites in DG SANTE's pesticide market approval procedure.

TABLE 4. EXAMPLES OF CARCINOGENIC PESTICIDE METABOLITES ON THE EU MARKET.

PESTICIDE NAME	CARCINOGENIC SUBSTANCE	ADVERSE EFFECTS OBSERVED	EFSA OPINION	COM DECISION	EU CITIZENS EXPOSED TO CARCINOGENS?
Carfentrazone-ethyl , herbicide classified C2 (likely carcinogen) by EFSA	Carfentrazone-ethyl	Thymoma	Drinking water limit exceeded by 4 metabolites while carcinogenic potential cannot be excluded	Approval with confirmatory data (CD) request for carcinogenic potential metabolites; the pesticide is on the market for decades already	In groundwater in some cases (winter cereals) above legal standard. In food generally at level of detection (0,01 - 005 ppm)
Maleic hydrazide	Hydrazine (impurity); Metabolite 3-pyridazinone of unknown potential	Classified carcinogen 1B and genotoxic	EFSA considers Hydrazine non-genotoxic at level of 0,028 ppm (threshold approach), a no observed effect level in a genotoxicity study	Approval. On the market for decades	Maleic hydrazide, by residues in food (potatoes, carrots, eggs, milk) while models are unclear about exceeding the groundwater standard. No information on environmental fate of Hydrazine
Thifensulfuron-methyl	Thifensulfuron-methyl and possibly the metabolite IN-A4098	Mammary tumours in rat studies	A LOAEL of 26 ppm was set, and because of a chronic NOAEL of 1,3 ppm, classification for carcinogenicity not considered necessary	Approval ("confirmatory data" procedure: applicant can deliver information on carcinogenicity at a later stage). On the market for decades.	Yes, by residues in food and drinking water; exceeds groundwater standard for pesticide and several of its metabolites; some metabolites are possibly carcinogenic
Mesotrione	AMBA, metabolite	AMBA positive in in vitro cytogenetic test and in vivo genotoxicity test	Genotoxic potential of AMBA needs to be clarified	Approval ("confirmatory data" procedure: applicant can deliver information on carcinogenicity at a later stage). On the market for decades.	Yes, by residues in food (animal origin, especially fed with genetically modified soybeans).
Flazasulfuron	Metabolites in humans, DMPU and HTPU, HTMU	Positive results obtained in the in vitro chromosome aberration test (genotoxicity)	Data gaps for metabolites; need to clarify the genotoxic potential of DMPU andHTPU with further in vitro tests; in vivo investigations needed for HTMU (groundwater pollutant) to see if the positive results can be overruled	Approved in 2004 (revision in 2018) On the market for decades.	Residues formed in humans by consumption of Flazasulfuron. Also residues in plants with unknown genotoxic potential (HTPP). Residues in groundwater water
Metsulfuron-methyl	Genotoxic potential (plant) metabolite IN-A4098 (triazine amine) and IN-B5685	IN-A4098 'equivocal' (positive?) results in in vitro clastogenicity assays and gene mutation assay; IN-B5685 positive in a chromosome aberration assay in vitro	Data gap for metabolite IN-A4098 (groundwater pollutant > 0,1 ug/L), " ; metabolite IN-B5685 EFSA feels no need to investigate because <0,1 ug/L in groundwater	Approved in 2016 with "confirmatory data", to "confirm" that (IN-A4098) is not genotoxic and not relevant for risk assessment . On the market for decades.	Yes, by residues (especially IN-A4098 and other metabolites in food of animal origin) and possibly in groundwater water (Metsulfuron and metabolites no information).
Iprovalicarb, C2, likely carcinogen	Iprovalicarb metabolite PMPA carcinogenic potential not excluded	C2 because of several types of tumours in rats; no data on metabolite	Use of Iprovalicarb (C2) declared safe at NOEAL; additional in vitro testing required for its metabolite to exclude genotoxic potential	Approved in 2016 with "confirmatory information" as regards the genotoxic potential of soil metabolite PMPA. On the market for decades.	Yes, by residues in food (grapes) for Iprovalicarb and metabolites, there is even a potential uptake by plants from soils in next year. PMPA exceeds the groundwater standard.
Halosulfuron-methyl	New active substance; still no information on its potential genotoxicity metabolite Chlorosulfonamide	In vitro gene mutation test showed health concerns	Genotoxic potential considered an "issue that could not be finalised"	Approved in 2013 with CD: "data to clarify the potential genotoxic properties of chlorosulfonamide acid". On the market since 2013.	Halosulfuron not above detection limit in food but present in groundwater. Chlorosulfuron is analysed in plants and in groundwater (data gaps).

PESTICIDE NAME	CARCINOGENIC SUBSTANCE	ADVERSE EFFECTS OBSERVED	EFSA OPINION	COM DECISION	EU CITIZENS EXPOSED TO CARCINOGENS?
Metosulam	Metosulam is a carcinogen (no classification) Unknown genotoxic potential of an impurity	Renal tumours for Metosulam.	Limited evidence of a carcinogenic effect for Metosulam. No information of genotoxic potential for the impurity ('issue that could not be finalised').	Approved in 2011 by imposing a 'safe level' for the carcinogen Metosulam. CD for the impurity. On the market since 2010.	No residues in food of Metosulam above the detection limit. Impurity unknown.
Buprofezin	Known genotoxic metabolite (Anilin).	Anilin classified M2, C2	While EFSA uses a threshold approach (MOE), it also states that exposure is an a priori concern since a threshold for a genotoxic carcinogen cannot be assumed.	Risk exposure to anilin not acceptable; only use on non-edible crops allowed. Operator exposure acceptable. Not approved in 2008, approved in 2011.	Exposure of operator, bystanders and residents to Buprofezin (and possibly anilin) accepted.
Diflubenzuron	Known genotoxicty of impurity and metabolite 4-Chloroanilin (PCA); unknown potential metabolite PCAA		EFSA concluded that potential exposure to PCA as a residue (i.e. either for consumers or for workers and bystanders/residents) should be considered a priori as a concern since a threshold for a genotoxic carcinogen cannot be assumed.	Risk exposure to PCA not acceptable; only use on non-edible crops allowed. Operator exposure acceptable. Approved in 2008.	Exposure operator, bystanders and residents to Diflubenzuron (and possibly PCA) accepted.
2,4-DB	Genotoxic potential of impurity and metabolite 2,4-DCP (dichlorophenol); presence Dioxin	Positive effects in genotoxicity tests	2,4-DCP in meat and milk.	Pending new decision. On the market for decades.	

Conclusion:

EFSA allows EU citizens to be exposed to genotoxic, carcinogen and chromosome damaging pesticide metabolites

EFSA's policy on using risk assessment for carcinogenic metabolites (in contrast to the hazard approach for active substances) contributed to that acceptable exposure

Sometimes EFSA's conclusions are contradicting, on Diflubenzuron a threshold for a genotoxic carcinogen cannot be assumed, while for Hydrazine EFSA assumes that below a threshold, the chemical is not genotoxic.

In case of uncertainty, additional testing is requested from the applicant ("confirmatory Information regime") while granted market access is continued and people possibly exposed to grave harm; a violation of the precautionary principle

5.4. EFSA WORKING GROUP ON THE MARGIN OF EXPOSURE (MOE) FOR IMPURITIES, 2012[34] (OWN INITIATIVE).

Despite a previous opinion (2005) stating that *"substances which are both genotoxic and carcinogenic should not be approved for deliberate addition to foods or for use earlier in the food chain, if they leave residues which are both genotoxic and carcinogenic in food"*, this EFSA groups is trying to change this opinion for impurities. They are encouraged by an opinion of the ANS panel on the use of MOE for impurities.

This working group now conclude: *"The Scientific Committee recognises that this is an important problem. Analytical methodology is continually improving, and an increasing number of impurities, including some which are both genotoxic and carcinogenic, can be detected at low levels in, for example, food/feed additives or food contact materials. As a result it can be foreseen that these impurities may end up in food, including products from animal origin. The Scientific Committee is of the opinion that the MOE approach can be applied to impurities which are both genotoxic and carcinogenic, irrespective of their origin"*.

This opinion is remarkable since they now allow genotoxic carcinogens to be deliberately added to food (through pesticide applications). It is difficult to understand what science lies behind this operation and it more looks like a service to pesticide industry. Instead of being happy that more impurities are detected, creating the opportunity to protect people, EFSA's solution is to conclude that these genotoxins are acceptable.

TABLE 5. COMPOSITION OF THE EFSA WG. ON MOE FOR IMPURITIES.

NAME	INSTITUTE	TYPE OF EXPERT	INDEPENDENCE
B Antunovic	Unv Zagreb	scientist	
A Barlow	-	consultant	Work for ILSI and (cigarette) industry
A Chesson	Univ Aberdeen	scientist	Review ILSI on GMO 2007
A Flynn	University College Cork (IE)		ILSI board of directors
A Hardy	Formerly Central Science Lab. UK	Scientist (no original publications)	Member industry lobby club ILSI taskforce 2008 - 2010
M Jeger	Imp Coll, UK	scientists	
A Knaap	National Institute of Public Health and the Environment (RIVM	Civil servant (retired)	ILSI, Unilever
H Kuiper	RIKILT, Wageningen	Civil servant	ILSI task force GMO
D Lovell	Uni of London		IWTG group, publication with industry ; industry consultant, worked for Pfizer
B Norrung			
I Pratt	Food safety agency Ireland	Civil servant	Chair ILSI wg. on MOE, review ILSI studies
I Rietjens	Wageningen Univ	Scientist	ILSI taskforce on AOP, consultancy for industry (Wessanen), BASF, Procter & Gamble
J Schlatter	Publ. Health Off. Switzerland	Civil servant (retired)	Member ILSI Europe Scientific Advisory Committee1999 – 2010; Member Board of Trustees ILSI 2008 – 2012; Member ILSI group 2004, mode-of-action with Kleiner, Kroes, Renwick, Piersma; ILSI Board of Directors 2005; Member ILSI group 2008 with Boobis, Meek, Renwick
V Silano	Portugal	Civil servant	
F Smulders	Austria	Civil servant	
P Vannier	France	Civil servant	

Conclusion:

The majority of the members of the EFSA scientific committee have links to commercial interest groups

This raises questions about why EFSA's scientific committee asked for this mandate; EFSA considered it an "important problem", but the solution is to allow market access, and thus there is no attempt to protect the public

5.5. EFSA GENOTOXICITY STANDING WORKING GROUP 2015–2018 (OWN INITIATIVE).

The objectives of the wg. are to support the different EFSA units/panels with the evaluation of genotoxicity data, esp. in case of different views, and advice on the interpretation of genotoxicity data from genotoxic testing, esp. in case of equivocal results.

All kinds of questions have been answered by this wg. like which test to be followed for the identification of genotoxic substances. Here the (own initiative) mandate on genotoxic mixtures is analysed.

Highlights are (quote from the minutes of the EFSA genotoxicity standing working group): *"First, the individual chemical-based approach should be applied to the part of the mixture containing known substances (known part). If there is a genotoxic compound in the known part of the mixture and if the respective concentration in the mixture is high enough to be of concern, the whole mixture is of concern. Note that it is a risk management issue to accept low concentrations of a genotoxic compound in a mixture or not. It is further noted that some substances are genotoxic or carcinogenic only via a particular route of exposure (e.g. formaldehyde by inhalation) and this consideration should be kept in mind during the assessment. If there is no genotoxic compound in the known part of the mixture, then it should be checked if the unidentified part is substantial (e.g. ≥10-20 % ?). At this stage, information about production process would also help to assess whether substances of concern might be present the unidentified part. With this additional information, it should then be possible to proceed assessing the mixture as a whole. Prior information on the mixture is, therefore, mandatory. "Whole mixture" approach should give also information on the interaction between the various components, whereas the individual-based approach does not provide this kind of information (e.g. what are we testing? what do we know about the single component?). It was suggested to prepare, for the next meeting, examples of assessment of mixtures in different areas (e.g. food and feed additives, botanicals, contaminants). Risk assessors can face 3 different situations: - no indication of genotoxicity in the mixture (is the mixture properly characterised?) - indication of genotoxicity for some of the components or for the unidentified part of the mixture - indication of genotoxicity in vitro of some components or for the unidentified part of the mixture but no information from in vivo tests. In this case, additional information about in vivo genotoxicity could be asked "*.

The 2018-opinion adds: "..to consider in the overall assessment positive test results *in vivo* that are obtained under conditions associated with overt toxicity, which are usually considered of limited relevance, as it cannot be decided whether the observed genotoxic effects are secondary due to cytotoxicity".

In conclusion, on the balance of considering protection for humans vs. considerations of no-harm (safety of the chemical), the wg. mostly argues in the direction of safety of the chemical:

1

There is no consideration of combined toxicity at all (cumulative effects);

2

Escapes from experimental positive in vivo genotoxicity tests are provided (secondary toxicity);

3

If a low level of genotoxic substance is present, it is of no concern (without proper justification or experimental results)

4

For genotoxic carcinogens, a MOE of 10.000 (a threshold that is 10.000 times higher than the toxic level) can be applied (while the same wg. agrees that DNA-reactive substance have no threshold)

5

In case no data are available for the genotoxic substance on carcinogenicity, TTC is applied (again a DNA-reactive substance can be approved if carcinogenicity studies are lacking; TTC is a threshold derived by the industry itself[35])

6

For mixtures without data, two in vitro tests are sufficient, Ames and vitro MN (no mentioning of the need to perform in vivo tests).

EFSA's selection criteria for the wg.:

Long standing experience in genotoxicity assessment in relation to the different areas of EFSA remit of activities, namely: food additives, food contact materials, food colourants, food enzymes, feed additives, contaminants, pesticides, GMO; involvement in EFSA's activities as members of the Panels/Units; Long standing experience in human health toxicology in relation to the different areas of EFSA remit of activities, namely: food additives, food contact materials, food colourants, food enzymes, feed additives, contaminants, pesticides, GMO

It is clear that academic scientists will fail to qualify on these criteria, and regulatory experts, with an EFSA background, will dominate the working group.

It is also remarkable to note that experts with a conflict of interest are invited to the wg. by the EFSA management: *"Jan van Benthem and David Kirkland have been selected as members of the Standing WG due to their aforementioned experience and their in-depth knowledge of in vivo and in vitro genotoxicity testing and carcinogenicity. They were also part of the WG that developed the Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment, and therefore, for continuity reasons, they are the preferred options for joining the standing WG on genotoxicity 2015-2018"*.

TABLE 6. COMPOSITION OF THE EFSA STANDING WG. ON GENOTOXIC MIXTURES, 2018.

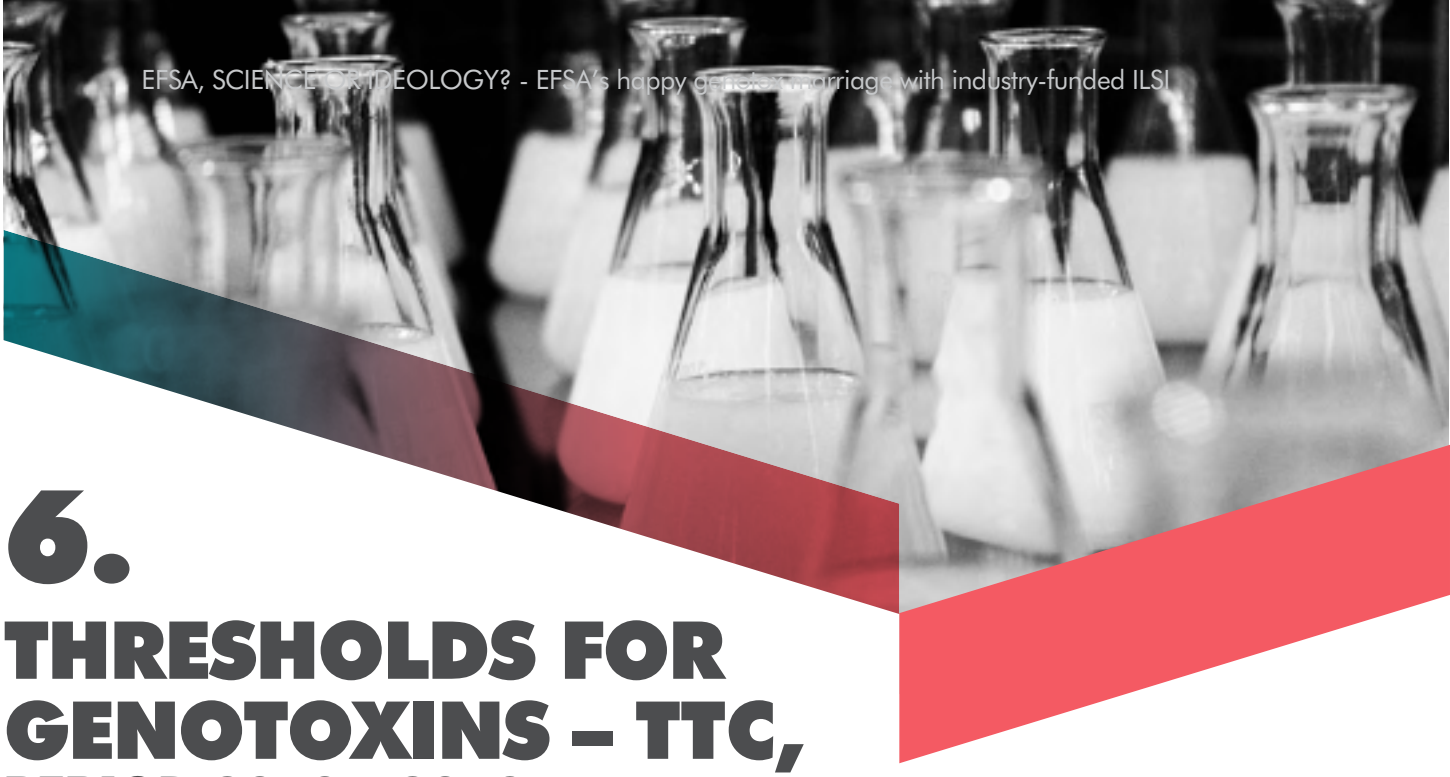
NAME	INSTITUTE	TYPE OF EXPERT	INDEPENDENCE
R Crebelli	Istituto Superiore di Sanità, Rome, Italy	scientist	IWTG wg. (industry chaired), publications with industry
D Benford	FSA, UK	Civil servant	Part of ILSI wg. on industry agenda such as, benchmark dose, MOE; published with industry consultants such as Schlatter and Renwick and industry such as Unilever and Nestle
J Schlatter	Swiss Federal Office of Public Health	Civil servant	ILSI board of trustees and long range of ILSI committees
P Mosesso	Dipartimento di Scienze Ecologiche e Biologiche, Università degli Studi della Tuscia, Viterbo	Univ	
R Guertler	Federal Institite for Risk Assessment (BfR)	Civil servant	
R Solecki	BfR, Germany	Civil servant	ILSI-HESI team mode of action; publications with industry (BASF, Syngenta)
G Aquilina	Istituto Superiore Sanità	scientist	
C Vleminckx	Scientific Institute of Public Health (ISP-WIV)	Civil servant	
E Nielsen	Denmark	Civil servant	
K Hirsch-Ernst	BfR, Germany	Civil servant	
S Grillo	DIMES Dept. Bologna Univ. Medical School	Univ	
J van Benthem	RIVM, NL	Civil servant (he was first a member, next a hearing expert, and finally again a member of the wg.)	Member wg. 2005; member ILSI wg. 2009; member ILSI Committee on genetic toxicology 2007-2012; chair of ILSI-HESI's Genetic Toxicology Technical Committee (GTTC) 2012- 2017; in 2018 author of ILSI publications
D Kirkland	-	Consultant (hearing expert)	Industry consultant, ILSI, EEMS, ECVAM
P White	Health Canada	Civil servant (hearing expert)	IWTG, publications with industry on "no observed genotoxicity levels") .

Conclusion:

Again in this own initiative mandate, many members are included with a questionable independence

It seems even an industry consultant that is active in this field for years, has been included as a member

At least half of the experts have a questionable independence



6.

THRESHOLDS FOR GENOTOXINS – TTC, PERIOD 2010 – 2019.

The MOE proposal (used by EFSA to grant market access to genotoxins) is discussed in the previous chapter, here we will discuss the TTC concept, a similar tool.

TTC (threshold of toxicological concern) is a fixed limit of human exposure and if the exposure to a certain chemical is below this figure/threshold, the chemical is classified as "safe" and no testing is needed. Most chemicals are placed in a group called Cramer III and EFSA assumes a level of 90 μg is safe for daily intake for adults. Lifelong. Some (smaller) groups have a higher TTC, some lower (nerve poison chemicals 18 μg/day, genotoxic carcinogens 9 μg/day). TTC is used already for flavouring chemicals. It is now, surprisingly enough, proposed by EFSA for chemical impurities and metabolites which industry is reluctant to test. The industry is pushing to extend TTC to all chemicals including those in REACH. This would save considerable testing costs.

TTC is constructed to ease the access of chemicals to the market and pays little attention to the protection of people's health.

Here are a few critiques:

The TTC uses regulatory (very) old narrow-focussed industry study data (NOEL's or LOEL's, no observed effect level or lowest observed effect) as a basis; EFSA did not check the original studies because they were non-retrievable (they could not be read, they are lost);

TTC accepts a certain level of harm to people by using a cut-off level (5th percentile) instead of the lowest available NOEL, allowing adverse effects of exactly the most toxic groups of chemicals;

TTC disregards independent scientific research on chemicals and the much lower data available (data from independent academics are not considered) to falsify these alleged industry "no-effect" data

TTC disregards chemical mixtures to which humans are exposed

TTC ignores effects on vulnerable groups like foetus and infants

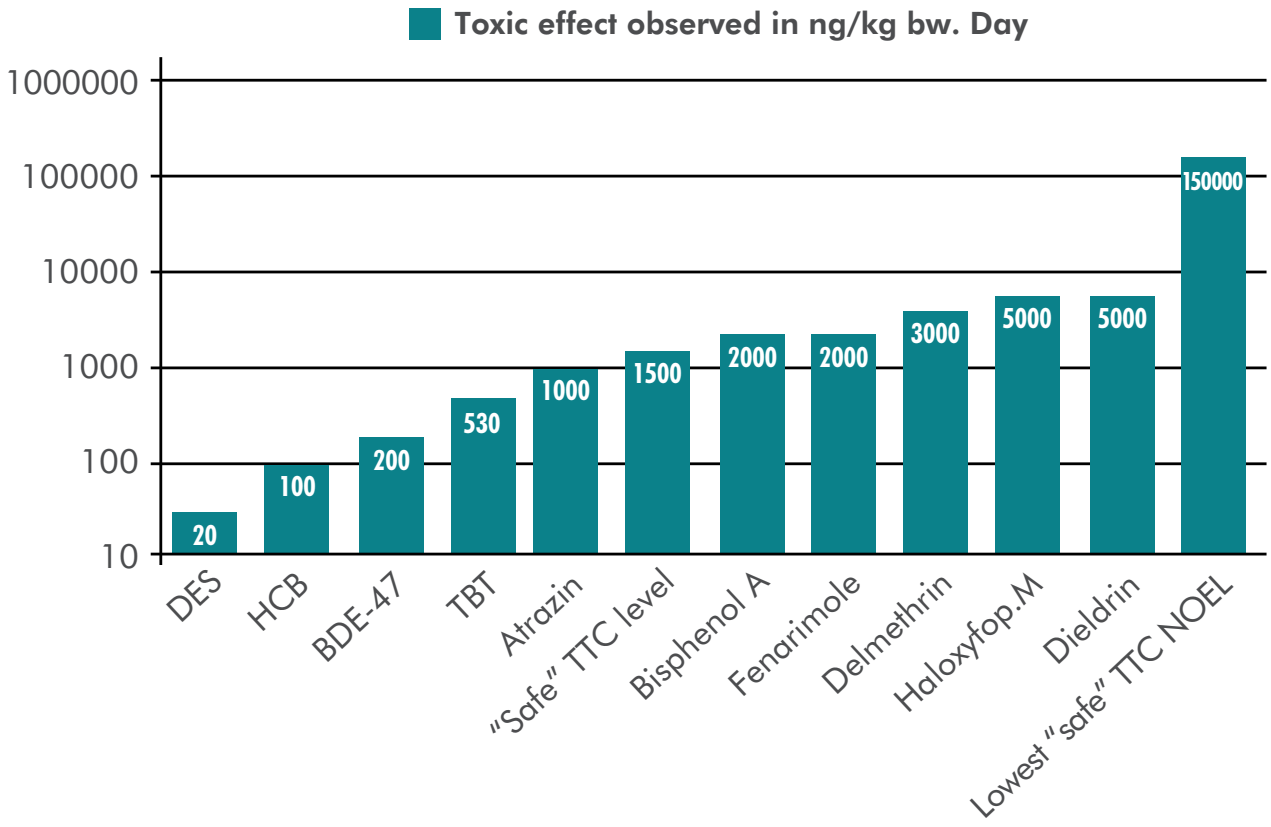
TTC allows lifetime human exposure likely calculating/estimating average intake, masking peak/acute doses

TTC disregards decades of scientific progress on vulnerable windows of exposure during development with epigenetic processes, EFSA even includes endocrine disrupting chemicals in these groups;

TTC once was intended and used only to get an indication of risk; now its proponents have crossed a line saying it is safe for humans and should be used in deciding on market access of pesticides.

In the original publication by Kroes and Galli in 2000[36], TTC was not designed for genotoxic carcinogens: *"The threshold principle is based on the assumption that at or below that threshold, homeostasis is maintained. This is, in essence, true for almost all toxicological endpoints, with the exception of genotoxic carcinogens where, for regulatory purposes, it is often assumed that the threshold does not exist"*. No threshold, no TTC. In a next publication with ILSI[37], a next line was crossed and genotoxic carcinogens (with some exclusions) were considered covered by TTC[38]. This extension to a completely different category of chemicals, genotoxic carcinogens, is not based on solid experimental results. It turns the principle that genotoxic carcinogens have no safe level into the opposite, safe levels of low risk do exist.

The 5th-percentile TTC cut-off disregards many low-dose negative health effects. If TTC-values (Cramer Class III) are compared to LOEL data from independent literature, for several chemicals (DES, HCB, BDE-47, TBT, Atrazine, see Annex I), effects are observed below the TTC-value. The EFSA claim on Cramer Class III (the majority of the chemicals) that "…it results in a TTC value that is approximately 3-fold lower than the lowest NOEL value…" – is a false claim, it is in fact more than75 times higher than a level at which effects are still observed (see graph below). Knowing that chemical testing is generally done at very high doses, low doses test outcomes are rare and generally only available in independent scientific studies. Noting the independent academic studies are disregarded in pesticide risk assessment[39], the TTC values EFSA/ILSI base themselves upon will not be representative. See also Annex I for example data of low dose health effects, as doses inferior to the levels accepted under the TTC approach.



6.1. CONTROVERSIES ON TTC.

WHAT ARE THE OPINIONS OF THE ACADEMIC COMMUNITY ON TTC?

The simple answer is they do not want to discuss TTC because it is highly unscientific. Some academic scientists are really upset about this tool that is claimed to be scientific. Most simply ignore it. Prof Millstone (Univ of Sussex) wrote to EFSA: *"Chronic uncertainties in the studies and databases that are included are not acknowledged, their relative weakness is not taken into account and no overall evaluation of uncertainty is provided. The draft conclusions and recommendations presuppose evaluative judgements, but the text is drafted in the rhetorical guise of factual statements, a tactic that also fails to comply with EFSA's stipulated guidance (on transparency of the scientific aspects of risk assessment). The EFSA/WHO draft on a possible Threshold of Toxicological Concern Approach, and the concept of a TTC itself, are un-scientific and anti-scientific. They are un-scientific because they constitute thinly-disguised corporate wishful thinking masquerading as if they are providing estimates of natural constants. They are anti-scientific because they are being invoked as grounds for not requiring firms to conduct or commission toxicological tests. The draft proposes to rule out a priori entire ranges of investigations; such studies are supposedly unnecessary as the authors of the draft document pretend that they already know what the results will show. While the idea of a TTC could be treated as a hypothesis for testing; using it as an excuse for insisting that no tests should be conducted is irredeemably anti-scientific"*.

WHAT DO FREE MARKET PROMOTORS THINK?

An ILSI monograph[40] puts it this way: *"The Threshold of Toxicological Concern (TTC) as described in this Monograph is a principle that refers to the establishment of a generic human exposure threshold value for (groups of) chemicals below which there would be no appreciable risk to human health. The concept proposes that such a value can be identified for many chemicals, including those of unknown toxicity when considering their chemical structures. Evidently the establishment of a more widely accepted TTC would benefit consumers, industry and regulators. For example, there is an ongoing concern that humans are exposed to a diverse array of chemicals and there is a demand to evaluate large numbers of chemicals. At the same time there exists a strong pressure to reduce our reliance on animal experimentation and to rely increasingly on in vitro and in silico data. Use of the TTC principle would eliminate the necessity of extensive toxicity testing and safety evaluations when human intakes of a chemical are below a certain level of concern, would focus limited resources of time, funding, animal use and expertise on the testing and evaluation of substances with greater potential to pose risks to human health and would considerably contribute to a reduction in the use of animals"*.

ILSI's rhetoric is astonishing: they are mentioning advantages such as the questionable advantages for consumers that will be exposed to chemicals that would otherwise be banned.

WHAT IS THE OPINION OF EFSA ON TTC?

This will be discussed below in the following chapters.

6.2. EFSA WG. 2010 – 2012, TTC FOR CARCINOGENS (OWN INITIATIVE).

The justification for TTC in the opinion is: *"In Europe, substances that are the active or primary ingredients in products added to or occurring as residues in food or feed are assessed, prior to authorisation, on the basis of dossiers that include the results of toxicity tests. A requirement for toxicity testing is appropriate for such substances. However, the use of such substances may also result in the presence in food or feed of low-level impurities, metabolites, breakdown and reaction products, on which there are few toxicological data. The continuing improvements in analytical sensitivity are also resulting in the detection of a growing number of chemical contaminants in food and feed at low concentrations, as well as in the identification of substances on which there are few toxicological data"*. Instead of being satisfied that, based on better analytics, chemicals are discovered in our food and we can remove/prevent them from the food to protect consumers, EFSA mainly seems interested in a way to get these chemicals legally accepted. As EU barometers regularly indicate, citizens are very much concerned about chemicals in food[41]. The EFSA has been founded to ensure high standards of food safety and protect consumers. The EFSA here once again indicates that they actively try to 'whitewash' the presence of chemicals in food, like on TTC.

The EFSA opinion (2012)[42] is, besides deriving a safe level for general chemicals, also deriving a safe level for genotoxic substances with a 'genotoxic alert', while excluding some 'potent' carcinogens (i.e. aflatoxin-like, azoxy- or N-nitroso-compounds, benzidines, hydrazines). Excluding highly potent carcinogens also conveniently increases the TTC for carcinogens. This artificial division is theoretical and futile, and quite misleading, since when TTC is used for unknown chemicals potent carcinogens might also be dealt with by TTC.

Please note that in a later EFSA opinion on the pesticide Maleic hydrazide (see Table 4, deliberately added to food) the metabolite of Maleic hydrazide, the "potent carcinogen" Hydrazine, was considered to have a 'safe level'. The conclusion could go either way, it seems.

The opinion puts it this way: *"For substances with a structural alert for genotoxicity, the TTC value of 0.15 µg/person per day was derived by Kroes et al. (2004). This value is sufficiently conservative to be used in EFSA's work, provided the structures already designated as high potency carcinogens are excluded from the TTC approach. The Scientific Committee is aware that further substances have been added to the Carcinogenic Potency Database since this value was derived. However, because a large number of substances were already in the Carcinogenic Potency Database, the Committee does not consider that the TTC value for substances with a structural alert for genotoxicity would change appreciably. The Scientific Committee has considered the possibility that a genotoxic metabolite could be produced from a parent substance. If such metabolites were to be predicted and considered relevant, then the TTC value of 0.15 µg/person per day should be applied. The Scientific Committee recognises that there is no general agreement at present on how to interpret the outcome from the currently available tools used to make such predictions, because they have a tendency to generate a large number of potential metabolites"*.

Without proper evidence, the EFSA wg. states that *"non-genotoxic carcinogens are considered to have a threshold"*, while confusing language is used to hide that also genotoxic carcinogens (including DNA-reactive agents) will be covered by TTC.

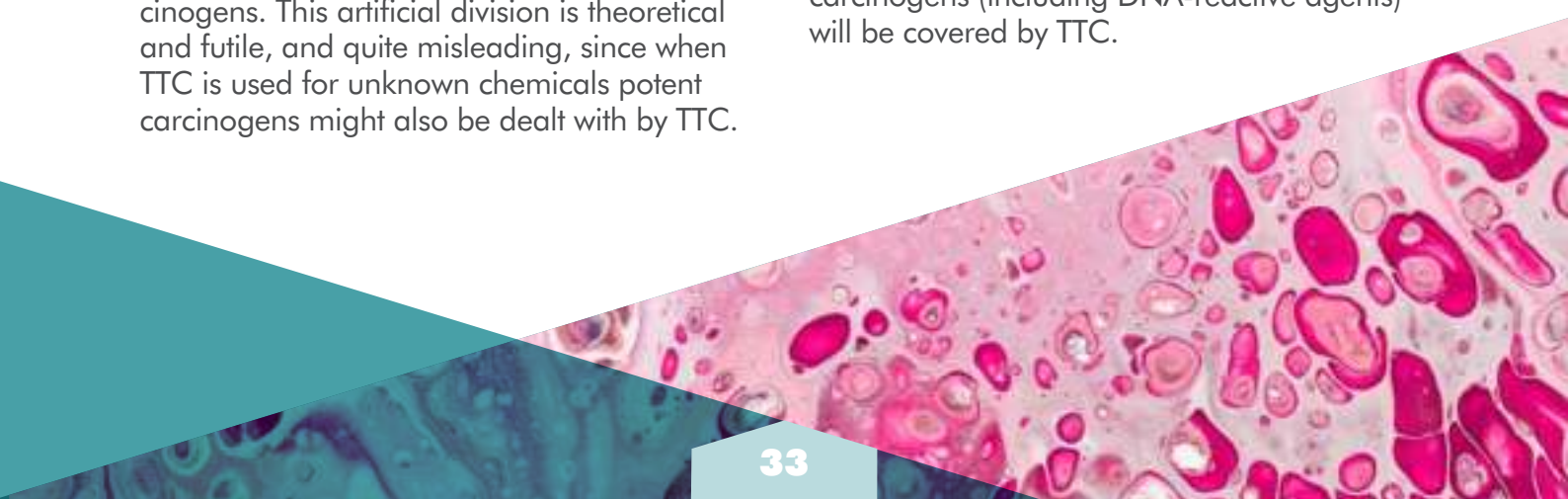


TABLE 7. COMPOSITION OF THE EFSA WG. ON TTC.

NAME	INSTITUTE	TYPE OF EXPERT	INDEPENDENCE
S. Barlow	-	consultant	Worked for ILSI, published with industry employees
A Boobis	Imperial College London	Scientist (retired)	Chair of Board of Trustees ILSI, several ILSI wg. TTC, RISK21 etc.; consultancy for industry AstraZeneca, Sumitomo, P&G etc.
C Galli	University of Milan	Scientist/industry consultant	Member ILSI TTC taskforce 2013 – 2016; Partner ILSI research program FOSIE 2002; publication with ILSI on TTC in 2000 and 2007; member scientific advice committee CEFIC 2013 – 2016; member Board of Directors ILSI Brussels 2013 – 2016;
U Gundert-Remy	Univ Berlin	Scientist (retired)	ILSI advisor 2005 – 2010; publication with P&G, Nestle and Unilever, and promoting TTC
JC Larsen	Danish Institute for Food and Veterinary Research	Civil servant	ILSI (scientific advisory committee)
A Piersma	RIVM	Civil servant	2003/2004 ILSI TTC working group (Kroes, Renwick, Kleiner, Cheeseman, Schlatter, Mangelsdorf eo.); 2008 ILSI-HESI steering committee toxicity screening; Piersma publishes regularly with industry employees
J Schlatter	Swiss Federal Office of Public Health	Civil servant	ILSI board of trustees and long range of ILSI committees
J Bridges	University of Surrey	retired scientist	ILSI board member
JC Lhugenot	Université de Bourgogne	Scientist (retired)	Promoted TTC in work for COLIPA; industry consultancy
D Lovell	Uni of London		IWTG group (industry-chaired), publication with industry ; industry consultant, worked for Pfizer
A Bulder	RIVM	Civil servant	
A Mantovani	Roma	scientist	
A Worth	EU-JRC	Civil servant	Expert group ILSI/COSMOS
G Zapponi	Istituto Superiore di Sanità, Rome	Scientist (retired)	ILSI wg. 1999
D Carlander	EFSA	Civil servant	Member ILSI taskforce on TTC

Conclusion:

The overwhelming majority of the EFSA wg. has a questionable independence[43]

The link of the experts with ILSI is clear, many of the experts actually designed TTC with ILSI

It looks like the chair, an industry consultant, invited her network for this wg.

6.3 EFSA-ILSI PARTNERSHIP MEETING 2011 ON TTC, INVITED-ONLY[44].

There is a close marriage between EFSA and ILSI is seems. No other stakeholders are invited for this meeting, except animal welfare groups. This is violating the EFSA rules on independence and transparency[45]. The justification for this meeting is unknown. Since the EFSA panels and wg. are already crowded by experts that have a link to ILSI, the EFSA TTC-wg. for a vast majority of the seats, then why would a closed meeting between the two be necessary?

Documents claim that the reason is: **"to overcome hurdles to acceptance of TTC"**. Apparently the public or politicians do not want to accept TTC and now EFSA and ILSI meet behind closed doors to make them swallow TTC.

After access to documents request, many of the names of the participants were blackened, but from the program, an impression could be obtained (see Table 8 below).

TABLE 8. INVITED EXPERTS TO THE EFSA-ILSI PARTNERSHIP MEETING 2011.

NAME	INSTITUTE	TYPE OF EXPERT	INDEPENDENCE
S Felter	Procter & Gamble	Industry employee	commercial
S Barlow	-	consultant	Work for ILSI and (cigarette) industry
A Tritscher	WHO	employee	Published many time opinions with industry
M Cheeseman	Food and Drug administration USA	Civil servant	Published with Kroes on TTC
AG Renwick	University of Southampton	scientist	ILSI task force
U Gundert-Remy	Univ Berlin	Scientist (retired)	ILSI advisor 2005 – 2010; publication with P&G, Nestle and Unilever, and promoting TTC
A Piersma	RIVM	Civil servant	2003/2004 ILSI TTC working group (Kroes, Renwick, Kleiner, Cheeseman, Schlatter, Mangelsdorf eo.); 2008 ILSI-HESI steering committee toxicity screening; Piersma publishes regularly with industry employees
L Edler	German Cancer Research Center (DKFZ)	Civil servant	Several ILSI working groups
B. Hubesch	CEFIC	employee	commercial
T Platzek	BfR, Germany	scientist	
I Dewhurst	FSA UK	Civil servant	ILSI taskforce, publications
T Wildemann	ILSI	employee	Industry funded institute
And.. employees from Coca-Cola, P&G, Danone, Nestle, Kraft food, CEFIC, DOW, DSM, Unilever, etc.			commercial

Conclusion:

The EFSA-ILSI meeting was totally inappropriate, excluding all other interest and the public at large

It was inappropriate because it aimed "**to overcome hurdles to acceptance of TTC",** a lobby target; it looks like EFSa is part of an advocacy group

Not the first time EFSA and ILSI had a 'partnership' meeting (in 2005 on genotoxic carcinogens, in 2014 on TTC).

6.4 EFSA-WHO REVIEW ON TTC, 2014.

This again was a strange meeting with the same core experts that designed TTC[46], the same that made its way to the EFSA panel and drafting EFSA's opinion on TTC[47], the same that organised an EFSA-ILSI TTC partnership meeting in 2011[48], excluding all stakeholder except animal welfare groups (that have the same mission as industry to get rid of animal testing) and finally the same being the ones that have been performing an EFSA-WHO 'review'[49] in 2014. Starting with a (fake) stakeholder meeting as a cover-up to the expert meeting, where again all stakeholders except industry and ILSI were invited and others (NGO's, independent scientists not invited) denied access. The outcome cannot be a surprise, with the original TTC-promotors at the steering wheel[50]. A proper conflict of interest policy was clearly lacking: *"The experts completed a declaration of interests and a declaration of confidentiality that were evaluated by WHO according to the organisations' rules"*, even 3 industry employees were invited such as Ms. Felter from Procter & Gamble.

A look at the composition of the 'expert' group tells the story. The same experts that designed and promoted TTC, got the opportunity as 'independent' expert to draft the EFSA opinion, and finally do the 'review' of their own work. A range of non-European civil servants got the opportunity for a meeting in Brussels. No independent academics nor top-level scientists were present. A masquerade EFSA unworthy.

TABLE 9. INVITED EXPERTS TO THE EFSA REVIEW OF TTC, 2014.

NAME	INSTITUTE	TYPE OF EXPERT	INDEPENDENCE
K Arvidson	FDA USA	Civil servant	ILSI expert group
G Barrett	Health Canada	Civil servant	ILSI expert group RISK 21, COSMOS-TTC
D Benford	Food Standards Agency UK	civil servant	2000 Author of ILSI monograph on acceptable daily intake; 2001 Author ILSI monograph risk assessment of food; 2008 ILSI workshop MOE (Rhodes); 2009 -2012 member ILSI Europe wg on benchmark dose (BMD); 2006- 2010 member ILSI Europe wg on margin of exposure (MOE); 2010 Author ILSI publication MOE, Food and Chemical Toxicology 48 (2010) S2–S24; 2014 meeting ILSI-HESI workshop on Genetic Toxicology
A Boobis	Imperial College London	Scientist (retired)	Chair of Board of Trustees ILSI, several ILSI wg. TTC, RISK21 etc.; consultancy for industry AstraZeneca, Sumitomo, P&G etc.
B Bruschweiler	Food Safety Office Switzerland	Civil servant	
M. Cheeseman	Steptoe & Johnson LLP	consultant	commercial
I Dewhurst	FSA UK	Civil servant	ILSI taskforce, publications
JL Dorne	EFSA	Civil servant	
M Dourson	TERA - USA	toxicologist	Commercial, ties to chemical manufacturers[51], tobacco companies and other industry interests, ILSI, Trump pick EPA
S Escher	Fraunhofer Inst Germany	Civil servant	
V Fattori	FAO	Civil servant	
M Feeley	Health Canada	Civil servant	
S Felter	Procter & Gamble	employee	commercial
U Gundert-Remy	Univ Berlin	Scientist (retired)	ILSI advisor 2005 – 2010; publication with P&G, Nestle and Unilever, and promoting TTC
K Jacobs	FDA USA	Civil servant	ILSI wg, TTC for cosmetics
SH Jeong	Oseo Univ	scientist	
X Jia	WHO	Civil servant	
D Kanungo	Min Agri India	Civil servant	
L Krul	TNO - NL	Civil servant	Worked for ILSI
E Leinala	OECD	Civil servant	
D Liem	EFSA	Civil servant	
Z Liu	FSA - China	Civil servant	
D Maurici	EFSA	Civil servant	Member ILSI taskforce on TTC
W Mennes	RIVM - NL	Civil servant	
U Muller	FSA - Nw Zealand	Civil servant	
OE Orisakwe	Univ Port Harcour-Nigeria	scientist	
AG Renwick	University of Southampton	scientist	ILSI task force
A Rossi	EFSA	Civil servant	
J Schlatter	Swiss Federal Office of Public Health	Civil servant	ILSI board of trustees and long range of ILSI committees
P Shah	US EPA	Civil servant	
A Tritscher	WHO	Civil servant	ILSI/FOSIE, publications with industry, worked for Nestle
T Umemura	NIHS - Japan	Civil servant	
C Yang	Molecular Network GmbH, Altamira LLC	consultant	Commercial, ILSI expert group

Conclusion:

The same network that designed TTC in industry-funded institute ILSI managed to get a seat in EFSA's working group on TTC (2010), to be invited to the EFSA/ILSI closed meeting in 2011, as well as to the "review" group in 2014, a total lack of independence

The 'review'[52] is hardly a surprise. Industry finally got what they wanted, a safe level for genotoxic carcinogens: *"The proposed TTC for genotoxic compounds of 0.0025 µg/kg bw/day, based on linear extrapolation for known genotoxic carcinogens, is sufficiently protective"*. Misleadingly adding that : *"Carcinogens that are not DNA reactive are adequately covered by the other TTC tiers"*, knowing very well that TTC is used for unknown chemicals and thus this exception is futile. Later in the text this is acknowledged *"For chemicals with genotoxicity alerts and hence possible DNA reactive carcinogens"* but only not taken care of, only writing: *"considerations were proposed to assure that an unknown peak does not represent a chemical from the TTC excluded classes. This could be done by considering prior information about the sample to judge whether specific 'TTC excluded classes' are likely to occur in a specific product. Then, exclusion based on chromatographic technique, sample preparation and/or detection method used or partial identification should be performed by targeted analysis and quantification of unidentified peaks"*. Totally unrealistic of course.

Based on a decades-old industry (non-independent) database the 'review' writes that *"The TTC value of 0.15 µg/person/day for potential genotoxic carcinogens based on structural alerts for genotoxicity (excluding aflatoxin-like, nitrosamine and azoxy-compounds; Kroes et al., 2004) was considered conservative because it was derived by linear extrapolation from the TD50 values combined with the analysis of the proportions of chemicals with each structural alert that had an upper-bound estimated lifetime cancer risk of greater than on in a million"*, putting assumption on assumption to reverse EU pesticide law that provides for "no contact to humans".

6.5 EFSA GUIDELINE ON TTC, 2019 (SCIENTIFIC COMMITTEE).

A final guideline on TTC and food safety was published by EFSA in 2019[53]. Confirming previous opinions n adjust making minor modifications. One remarkable one is that the "potent carcinogen" Hydrazine that was excluded from TTC, is now included : *"Hydrazines are no longer excluded from the TTC approach because only 4% of them (2 out of 57 hydrazines) exceed a cancer risk of 1 in 106 at an intake of 0.0025 lg/kg bw (i.e. the TTC value for potential DNA-reactive mutagens and/or carcinogens)"*. Again EFSA is not concluding based on science, but in fact takes political decisions that are not in its remit.

Also critique on using TTC for children is commented in the Guideline, *"Infants and children have a higher food intake per kilogram body weight than adults, and also have other dietary habits and food preferences, and therefore, it is important to take these into consideration when making exposure estimates for the TTC approach. In addition, infants and children are considered to be more sensitive to some toxicological insults than adults (e.g. the metabolic capacity and the renal function is two- to threefold lower in infants under the age of 16 weeks than in adults)"*. But as we have seen in Table 4, there is no special assessment for children (let alone for the unborn!), and the Guidance text looks futile.

The authors of the Guidance are familiar names like Benford, Schlatter, Gundert-Remy, Kleiner, all promotors of TTC from the start.

7.
ANALYSIS EFSA'S WORK ON THE CRITERIA FOR ENDOCRINE DISRUPTION, PERIOD 2013 – 2018.

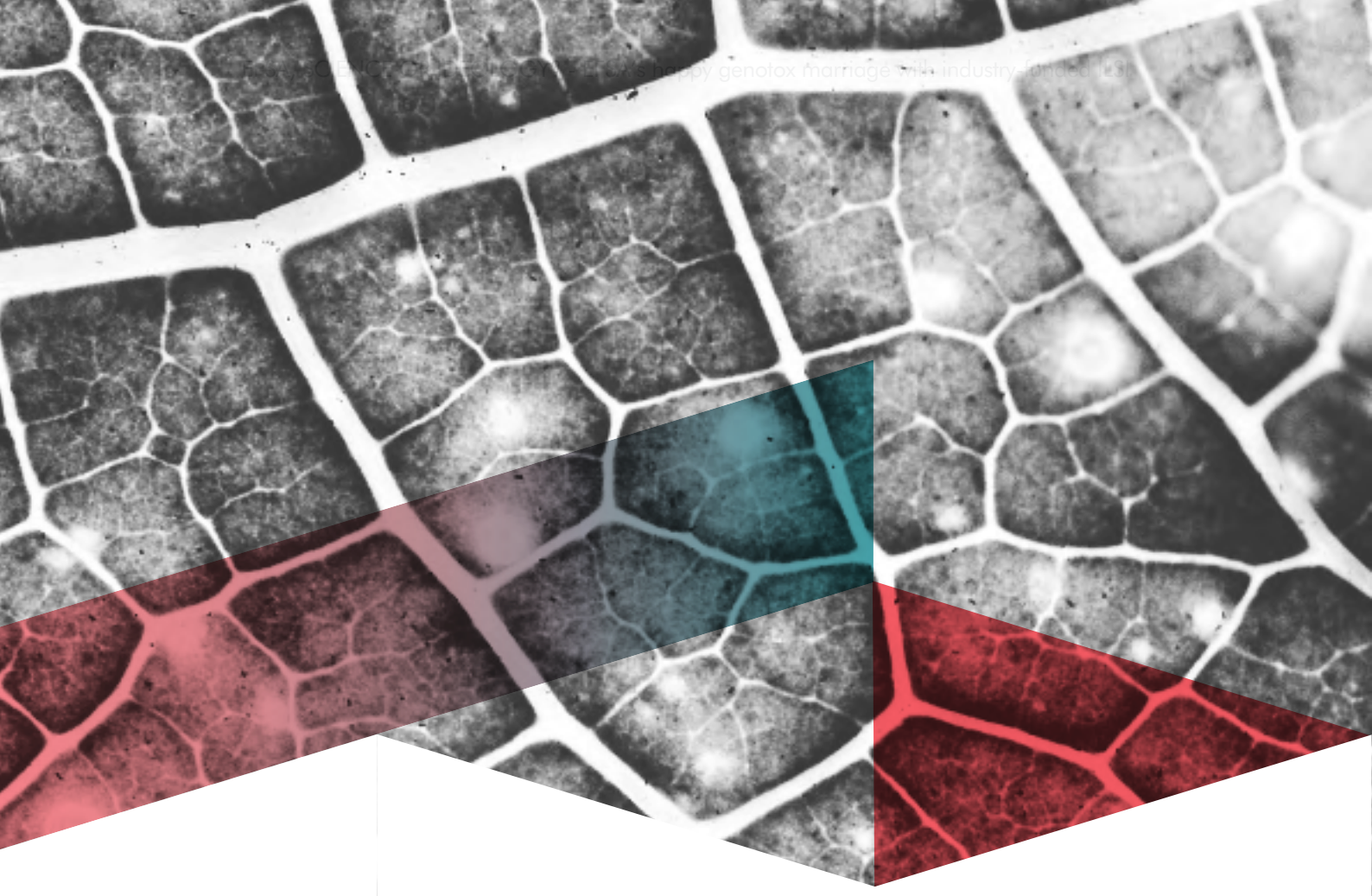
7.1. CONTROVERSIES ON ENDOCRINE DISRUPTION.

7.1.1 WHAT IS THE POSITION OF THE SCIENTIFIC COMMUNITY ON ENDOCRINE DISRUPTION?

The professional organisation of endocrinologists, the Endocrine Society with 18.000 academic members, published several reviews on endocrine disruption[54].They point out that endocrine disruption overturns the very concept that traditional risk assessment is based on: "the dose makes the poison". This is for the simple reason that hormone signals (or their disruption) are designed to be more potent at low than at high dose. In fact, receptor production often shuts off and the signal stops above a very low dose. In contrast, in traditional risk assessment, for reasons of costs, chronic toxicity tests use almost-poisonous doses and extrapolate downward (instead of testing). The solution is to require testing of far greater part of the area of the dose/response curve, especially the (realistic) dose that we, as humans, experience.

The Endocrine Society also insists that all tests should dose animals during development, as that is biochemically far more complex than adulthood and therefore very vulnerable. Critically also, animals should not be killed at human equivalent of 60 years old, or one will find only part of the diseases caused by the chemicals as shown by tests conducted by the Ramazzini Foundation[55].

Standard toxicity testing of chemicals is focussed on well-known effects like mutagenicity and carcinogenicity. Mental disorders and effects on metabolic processes (which might lead to obesity and diabetes, particularly as a result of exposure during developing life) are among the most obvious endocrine disruption related endpoints which are missing in current tradi-



tional toxicity testing. But the endocrine system requires much more endpoints like negative effects on the thyroid system, effects manifesting in old age, diabetes, obesity, etc. to fully include the potential effects of disturbing the endocrine system. A full mapping of the known elements of the endocrine system, hormone production, windows of vulnerability and potential endpoints of adverse effects is a necessary starting point for drawing up data requirements and determining necessary tests. Recent findings like the role of placenta hormone serotonin in neurodevelopment of the foetus and the role of bone hormone osteocalcin in fertility need to be taken into account as well. Additionally, many of these signalling pathways interconnect with one another (creating "cross talk"), is another element to be taken into account in testing.

A new testing system for chemicals with endocrine disrupting properties should start by learning from independent scientists how effects of endocrine disruption can be discovered in studies. Taking into account exposure during a special window of vulnerability (which may be different for different chemicals and different developing biochemical processes) is one element. Doing tests at low doses is another. Choosing the right test animal and the right strain also counts. Many chemicals with endocrine disrupting properties act at (very) low doses. The traditional idea of relying on the threshold linear dose-response curve does not work for many chemicals with endocrine disrupting properties. In several cases, chemicals with endocrine disrupting properties have been proven to act according to a non-monotonic, inverted U-shaped dose-response

curve[56]. Some examples of such a non-linear dose-response curve: High neonatal doses of the anti-miscarriage drug DES cause weight loss in new-born mice, while low doses caused obesity in later life[57].

Rat experiments on DEHP, a phthalate found in plastics, show that low doses suppress an enzyme needed for proper development of the male brain, while high doses stimulate the enzyme[58]. The well-known drug tamoxifen, given to treat certain breast cancers, is known to have opposite effects at different levels in the body.

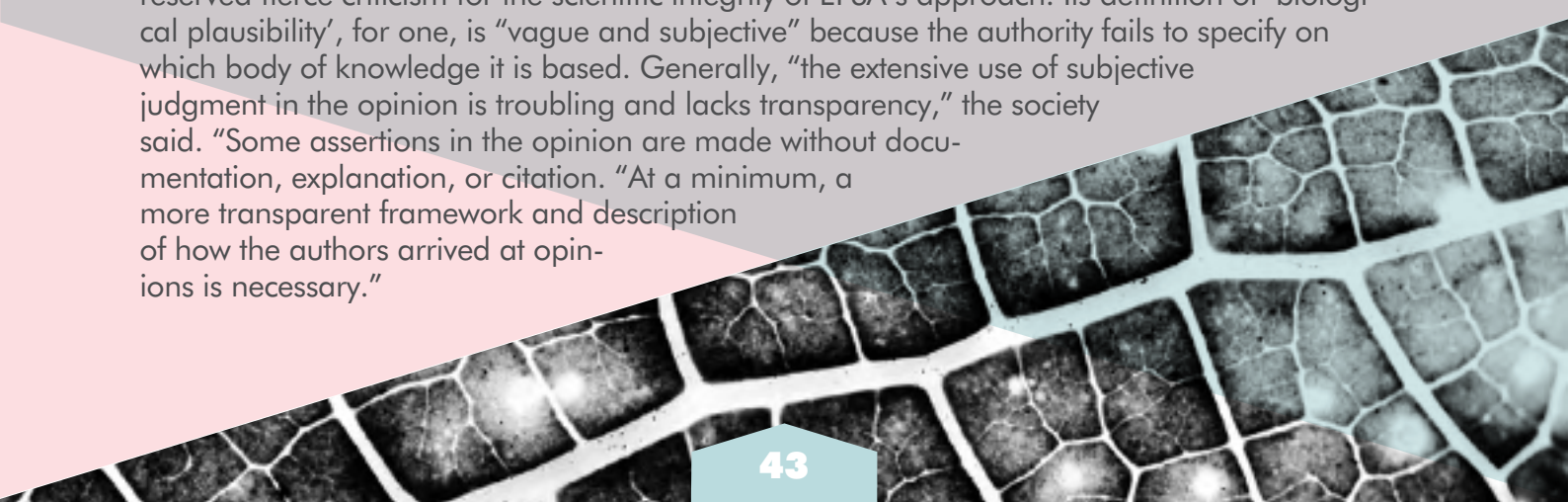
Chemicals with endocrine disrupting properties require special treatment which should be based on elimination of exposure wherever possible because it has been shown that chemicals with endocrine disrupting properties which act on the same target organs can have additive effects. A single substance risk assessment approach, which did not take into account the 'mixture effect' would not result in the protection of the public or the environment.

Hundreds of studies of independent scientists in academic laboratories show how a broad selection of chemicals can interfere with the normal development of offspring at extremely low levels of exposure (Bisphenol A, Chlorpyrifos, Mancozeb, etc.). These studies were done with the knowledge that the embryo and foetus develop under the control of hormones at parts per billion (μg/kg) and parts per trillion (ng/kg), and that as the baby matures, hormone concentrations are regulated by sensitive, thermostat-like feedback control systems in the brain.

Theo Colborn, author of the book "Our Stolen Future" and founder and president of TEDX, has called for a radical change of the testing battery, running tests at very low doses, checking all organs and tissues and systems that make up the endocrine system. She has further highlighted that expert scientists, working at the cutting edge of research into endocrine disruption should be given the opportunity and wherewithal to design a couple of comprehensive multi-organ assays to detect the most sensitive alterations in embryonic and foetal development and function, and that the various tissues from such a test should be sent to known experts in that field. We suggest that the European Commission takes a look at this approach and considers its adoption in EU-practices. In particular, the "critical window of development" approach needs special consideration.

WHO/UNEP published a scientific consensus document[59] on endocrine disruption, with best available endocrinologists, and concluded among others that *"developmental exposures can cause changes that, while not evident as birth defects, can induce permanent changes that lead to increased incidence of diseases throughout life. These insights from endocrine disruptor research in animals have an impact on current practice in toxicological testing and screening. Instead of solely studying effects of exposures in adulthood, the effects of exposures during sensitive windows in foetal development, perinatal life, childhood and puberty require careful scrutiny"*. And: *"For many endocrine disrupting effects, agreed and validated test methods do not exist, although scientific tools and laboratory methods are available. For a large range of human health effects, such as female reproductive disorders and hormonal cancers, there are no viable laboratory models. This seriously hampers progress in understanding the full scale of risks"*. And: *"A focus on linking one EDC to one disease severely underestimates the disease risk from mixtures of EDCs. We know that humans and wildlife are simultaneously exposed to many EDCs; thus, the measurement of the linkage between exposure to mixtures of EDCs and disease or dysfunction is more physiologically relevant. In addition, it is likely that exposure to a single EDC may cause disease syndromes or multiple diseases, an area that has not been adequately studied"*. All pointing out that traditional risk assessment will fail detecting endocrine disruption. The report is drafted by independent top-level scientists that have worked for a big part of their career on endocrine disruption.

The Endocrine Society in a recent letter to EFSA again criticized the Food Authority of not taking into account recent scientific insights, this time on non-monotonic dose-response curves. The Endocrine Society has called for "substantial revision" to the European Food Safety Authority's (EFSA's) draft approach for assessing non-monotonic dose-response (NMDR) relationships for chemicals. As it stands, the proposal is "an inaccurate assessment" that "will limit the ability of regulatory agencies to make health-protective decisions". The criticism came in response to a draft Opinion[60] of EFSA's scientific committee covering the biological plausibility of NMDR relationships. In the draft report, the EFSA scientific committee concluded there is currently no gold standard for statistical analysis of NMDR relationships for chemicals. It suggested a stepwise process for addressing NMDR relationships in risk assessment. For low-dose toxicity, it asked whether the effect is observed in a whole organism (apical) and supported by further experimental work. If not, further investigations are needed, it said. But EFSA's report "fails to acknowledge that NMDRs are well-defined mathematically, have been demonstrated to occur, and are well understood based on basic research of endocrine systems and hormone biology," the Endocrine Society wrote in its comments[61]. "NMDRs can and should be assessed statistically." The society slammed EFSA for not including endocrine scientists in the drafting process, even though most reported NMDRs are for endocrine disruptors. As a result, the report "fails to consider and incorporate scientific principles of endocrinology" and "does not reflect the latest scientific consensus", the society said. It called on EFSA to collaborate with the wider scientific community before the final version of the report is adopted. And the comments reserved fierce criticism for the scientific integrity of EFSA's approach. Its definition of 'biological plausibility', for one, is "vague and subjective" because the authority fails to specify on which body of knowledge it is based. Generally, "the extensive use of subjective judgment in the opinion is troubling and lacks transparency," the society said. "Some assertions in the opinion are made without documentation, explanation, or citation. "At a minimum, a more transparent framework and description of how the authors arrived at opinions is necessary."



7.1.2 WHAT DO FOLLOWERS OF THE 'FREE MARKET' IDEOLOGY CONCLUDE?

Pesticide industry umbrella group ECPA (recently re-branded "CropLife Europe") 's main claim is that the scope and nature of current testing is sufficient to detect adverse effects resulting from endocrine activity, to characterize these adverse effects in terms of a dose response and to provide reference doses that can be used in a risk assessment[62]. ECPA points at EFSA and states that its Scientific Committee has reviewed whether the current testing approach is fit for purpose and concluded that *"As for any other (eco)toxicological hazard, endocrine mediated adverse effects may be identified in standard toxicological tests that are routinely performed to fulfil the requirements of various regulatory programmes. In particular, endocrine-mediated toxicity may be detected in repeated-dose, reproductive and developmental toxicity, and carcinogenicity studies"*.

ECPA is concerned that the endocrine disruption criteria linked to the hazard based cut-offs in Regulation 1107/2009 could remove a significant number of active substances from the market without providing any demonstrated benefits to the protection of human health or the environment[63]. ECPA further states: "Several EU bodies have investigated the potential impacts of the cut-off criteria for endocrine disruption, including KEMI (Sweden) and the former UK Pesticide Safety Directorate" (PSD, now called the Chemicals Regulation Directorate, CRD) The most thorough analysis and the one likely to most accurately represent the impact of the ED criteria currently proposed by DG Environment, is the evaluation undertaken in 2009 by PSD[64]. PSD identified 13 active substances as *"most likely to be eliminated"* and a further 25 substances *"which may be eliminated"* by the ED cut-off criteria. This provides a total of 38 substances[65] which may be removed from the market out of the 286 assessed (representing approximately 13% of currently approved substances in the EU).

Another advocacy group[66] started attacking academic scientists by framing their work as "pseudo-science", for example by questioning claims that endocrine disruption is linked to obesity and type 2 diabetes[67] are without proper evidence. The group claims that the risk to humans at current levels of exposure would be negligible. In their views it makes no sense to override such evidence with a blanket ban on potentially hazardous chemicals that ignores the public's demonstrable low level of exposure. Conventional risk assessment, considering anticipated exposure levels, will be protective of both human and ecological health[68,69].

7.1.3 WORK OF EFSA, WORKING GROUP ON CRITERIA, 2013

The EFSA working group concluded that *"… to inform on risk and level of concern for the purpose of risk management decisions it is the opinion of the SC that risk assessment (taking into account hazard and exposure data/predictions) makes best use of available information. EDs can therefore be treated like most other substances of concern for human health and the environment, i.e. be subject to risk assessment and not only to hazard assessment"*[70]. And thus sees no reason to treat endocrine disruptors as a special category of chemicals as the Regulation does.

On much discussed topics related to endocrine disruption EFSA takes the following position:

Critical windows of susceptibility: notes that generally these vulnerable windows are not tested, only in the fish lifecycle tests;

Combined exposure to multiple substances: recognises that such an exposure could occur, but this will be addressed by EFSA in a separate activity;

Low-dose effects and non-monotonic dose response curves (NMDRCs): claims lack of consensus in the scientific community. Also in a more recent opinion[71], EFSA acknowledges the existence of these curves, but maintains its views:

"Overall, in evaluating a substance for which information on NMDR relations for one or more outcomes is obtained, the current risk assessment approach based on evaluating adverse outcomes seen in standard animal tests (as well as other observations) remains valid".

In general EFSA's position is close to a copy of industry's position[72] and lobby groups with a related ideology[73], which come down to the argument that traditional risk assessment can do the job (and apparently did the job in the past 30 years), and that there is no concern needed for endocrine disruption of pesticides.

One member of EFSA's group, after having read the WHO/UNEP report, and concluding that this is a balanced report with all current knowledge on endocrine disruption, including the majority of the scientists that have been most prominent in this field over the past 15 years, complained to the group as following: "..it is almost embarrassing to read our current draft (EFSA opinion) with the UNEP-WHO report. The issues the WHO-UNEP report highlights, we in our report trying to downplay or even avoid. When UNEP-WHO comes to the conclusion that traditional risk assessment is not fit for purpose to assess endocrines, we are coming to exactly the opposite conclusion. When UNEP-WHO takes out the importance of low dose effects and non-monotonic dose-response curves as being particular with respect to endocrine responses, we stay at best 'lukewarm' to these topics. And ends by saying that we (EFSA wg.) have to redo the report or at least significantly revise it.

EFSA's employee Bottex replies that the wg. should insist on the hazard approach being replaced by risk based approach.

The EFSA Scientific Committee also provided the following further clarification: *"Despite the fact that the existing internationally standardised assays might miss some endocrine-sensitive endpoints, this should not necessarily lead to the non-identification of endocrine disruptors. Given the complexity of the endocrine system with its multiple signalling pathways and cross-talks, an ED is expected to produce a pleiotropic response with a range of effects, some of which are likely to be observed in an appropriate guideline study"* (EFSA 2013).

In 2018 EFSA published a Guidance on the identification of endocrine disrupting pesticides[74]. Now EFSA didn't manage to stop the 'hazard approach' for endocrine disrupting pesticides, an effort was made to make identification of an endocrine disrupting pesticide difficult. Only when 3 types of information is available (endocrine properties, endocrine adverse effect & the link between those two), identification will follow. Note that for any other chemical the demonstration of an adverse effect is enough for a ban.

7.2. ANALYSIS OF THE COMPOSITION OF THE EFSA WORKING GROUP ON (THE CRITERIA FOR) ENDOCRINE DISRUPTION.

TABLE 10. COMPOSITION OF THE EFSA WORKING GROUP ON ENDOCRINE DISRUPTION (CRITERIA).

NAME & TITLE	INSTITUTE	TYPE OF EXPERT (OWN QUALIFICATION)	ACTIVE SCIENTIST[75]	EXPERIENCE ENDOCRINOLOGY	MAMMALIAN ENDOCRINOLOGIST/ CLINICIAN?	INDEPENDENCE[76 77 78]
1. Jan Alexander (prof)	Inst. Publ. Health Norway	Medical doctor/ toxicologist	Yes (research on food contaminants)	No	No	-
2. Josef Schlatter (dr) - retired	Publ. Health Off. Switzerland	Toxicologist	No (many comm. and opinions published with other industry-linked people such as Boobis, Barlow, Renwick, Kroes & ind. employees)[79]	No	No	13 years involvement in ILSI in various wg. and also member of ILSI Board in last 4 years; consultancy for many companies in food and drink industry
3. Robert Luttik (dr)	Dutch Health Inst.	Eco toxicologist	No	No	No	-
4. Anthony Hardy (prof) - retired	Formerly Central Science Lab. UK	Scientist	No original publications	No	No	Member industry lobby club ILSI taskforce 2008 - 2010
5. Diana Benford (dr)	Food standards Agency, UK	Civil servant	No	No	No	Part of ILSI wg. on industry agenda such as, benchmark dose, MOE; published with industry consultants such as Schlatter and Renwick and industry such as Unilever and Nestle[80]
6. Daniel Pickford (dr)	Brunel university	University Lecturer	No	Yes, few studies on amphibians	No	Worked for AstraZeneca till 2003; consultancy for Syngenta in 2009 and represented chemical industry (BIAC) in OECD on endocrines in 2001.
7. Peter Matthiessen (prof) - retired	Formerly UK environm. Institute CEH	Eco toxicologist	Yes	Yes, studies aquatic organisms	No	Consultancy for industry (RSA)
8. Karen Hirsch-Ernst (dr)	German risk assessment institute BfR	Toxicologist	No	Yes, co-author of a few in-vitro rat studies	No	Ms. Hirsch defends the German opinion on the criteria (published as a scientific article)[81]
9. Susanne Hougaard-Bennekou (dr)	Danish EPA	Toxicologist	No	Yes, not as a scientists but as a regulator	No	-

NAME & TITLE	INSTITUTE	TYPE OF EXPERT (OWN QUALIFICATION)	ACTIVE SCIENTIST	EXPERIENCE ENDOCRINOLOGY	MAMMALIAN ENDOCRINOLOGIST/ CLINICIAN?	INDEPENDENCE
10. Suzy Brescia	HSE, UK authorisation body	Regulatory toxicologist	No	No	No	Ms. Brescia defends the UK position that argues against the hazard approach on endocrines
11. Gisela Degen (prof)	Leibnitz Res. Centre occupational health, Germany	Toxicologist	Yes	Yes, much work on cadmium as estrogen	Yes	Worked for CEFIC on phyto-oestrogens
12. Peter Hoet (prof)	KU Leuven, occ. health, Belgium, works on nano-materials and air pollution	Researcher & teaching	Yes	No	No	-
13. Wim Mennes (dr)	RIVM, NL	Toxicologist	No	No	No	-
14. Thomas Platzek (prof)	BfR, German RA institute, consumer products	Toxicologist	No	No	No	-
15. Peter Pärt (dr)	JRC, Ispra	Seconded expert	No	No	No	-
16. Emanuela Testai	Institute Sup. di Sanita, consultancy for ministry Italy	Senior researcher	Yes	Yes, div. effects of pesticides on development, chlorpyrifos, atrazin, lindane	Yes	Ms. Testai is part of a pressure group[82] (Galli, Piersma ao.) that opposes the EU hazard approach
17. Theo Vermeire	RIVM, NL	Risk assessor	No	No	No	-
18. Jacques Auger	APHP, public hospitals, France	Reproductive biologist	Yes	Yes, male reproductive system/ vinclozolin	Yes	-

7.3. CONCLUSIONS:

1

The position of the EFSA wg. Is very similar to the positions of commercial interest groups and related experts

2

The position of EFSA opposes the views of the professional endocrinologists of the Endocrine Society on many points, low dose effects, special windows of vulnerability, hazard approach, non-monotonic dose-response effects, etc.

3

Only 3 out of 18 (17%) members of the EFSA wg. are mammalian endocrinologist/clinician and thus actively working in the field of endocrine disruption

4

Just 6 out of the 18 (33%) members are active scientists

5

11 out of 18 (61%) members have no experience whatsoever on endocrinology

6

5 out of 18 (28%) members are from UK, a country well-known to oppose the endocrine cut-off criteria (UK has voted against the Regulation)

7

Industry-linked people are included as a member, even an industry consultant with a long track-record of working with industry

8

The German representative (Ms. Hirsch-Ernst) and UK-representative (Ms. Brescia) cannot operate independently and are known to defend the joint German/UK position opposing the hazard approach of Regulation 1107/2009.

9

Requests to upgrade the work to a higher level (UNEP-WHO), in line with the current scientific knowledge is being arbitrarily dismissed by EFSA.

8. EFSA'S MANAGEMENT BACKGROUND

The selection process of experts in panels and working groups is officially done by EFSA management. Since EFSA does not provide documents on the selection (or hides them from the access to documents requests), it is difficult to find out how this selection is done.

To get an impression of the scientific background or a potential ideologic background of the EFSA management, a short assessment is done below based on "declarations of interest" obtained from EFSA in an "access to documents" request, obtained with the help of the EU Ombudsman[83]:

TABLE 11. BACKGROUND EFSA MANAGEMENT.

NAME & COUNTRY	POSITION AT EFSA	EDUCATION	INDEPENDENCE	EXPERIMENTAL SCIENTIST? (PUBMED & SCIENCE DIRECT SEARCH)
1. Bernhard Url - Austria	2008-2012 EFSA Management Board; 2012-2014 Director Risk assessment unit, 2014- present Director	Veterinarian		NO, no scientific publications
2. Marta Hugas	Chief scientist	Food microbiology, PhD	Visitor of ILSI-IFAP meetings and ILSI-meetings	NO, About 20 publications, mainly EFSA opinions; few experimental studies;
3. Juliane Kleiner - Germany	Senior science coordinator - start 2004	Food safety, PhD	Publishes with industry while employed by EFSA, mainly on thresholds for carcinogens and other safe levels[84]; came through the revolving door in 2004; she worked many years for industry lobby group ILSI (employee, 1996-2004) on risk assessment topics, advocating industry's views[85]	NO, publications with industry-linked experts, during her ILSI-period and also at EFSA; very few experimental studies (during PhD)
4. Alberto Spagnolli	Senior policy advisor	Economy, MsC		NO, no publications; civil servant at Commission for many years

NAME & COUNTRY	POSITION AT EFSA	EDUCATION	INDEPENDENCE	EXPERIMENTAL SCIENTIST? (PUBMED & SCIENCE DIRECT SEARCH)
5. Hubert Deluyker (retired)	Science advisor - start 2004, now retired	Veterinarian	Part of the MEP-Girling lobby group to stop the EU hazard approach and substitute it by a 'safe level' approach; came through the revolving door in 2004, worked for Pfizer, Belgium, Pharmacia and Upjohn	Dozens of publications on animal diseases and vaccination before 2004, mainly in Belgium journals
6. Hans Verhagen	HoD risk assessment - start 2015	Chemist, worked for Dutch RIVM for many years	Cooperated with ILSI and industry in FP7-program BRAFO 2007-2013 (cost-benefit analysis) and industry-linked experts like Boobis; Editor FCT, an industry captured journal; worked for Unilever in the past; attended several ILSI meeting from 2002 - 2015.	A few dozens of experimental studies published; and a range of opinions
7. Guilhem de Seze	HoD Sc evaluation products - start 2016	Chemical engineering PhD	Worked for chemical industry ("in the field of hazardous chemicals management in academia and in the chemical industry for over ten years")	NO, few publications
8. Barbara Gallani	HoD communications - start 2016	Adv Instrum Science, MsC	Came through the revolving door in 2016 from UK food industry lobby group Food and Drink Federation (Director)	NO, no experimental work, few opinions for FDF; previously worked for consumer organisation BEUC
9. Jose Tarazona		Veterinaire	Worked for many years for industry lobby group CEFIC, defending; 'safe' thresholds (for POP's)	
10. Bernhard Bottex			Worked for ILSI, came through the revolving door to EFSA	
11. Didier Verloo	Head of Assessment and methodological support Unit	Veterinaire, Belgium research institute	In board of trustees EBTC, with many industry links; In advisory board of CAAT (link to EBTC)	
12. Tobin Robinson	Head of Scientific Committee and Emerging risks Unit		Worked for Danone, in 2006 direct to EFSA	
13. James Ramsay	Head of communication unit		Worked for MPR consulting: "Our consultants possess strong industry background with hands-on operational implementation experience".	

Conclusion:

Several EFSA managers have past links to industry

Some even came through the revolving door from industry or industry funded groups, including ILSI

11 out of 13 EFSA employees assessed have a questionable independence

9. DISCUSSION

The selection of experts for EFSA's panels and working groups largely remains a black box. Access to documents request of PAN Europe to EFSA has not shed any light on the actual procedure applied. The selection should be transparent and the management board should be accountable but this is not the case. Selection criteria[86] are very general like a 'mix of competence' (Art.8). Art. 1 even mentions as a criterion "scientists" without clarifying if these are active scientists or scientists that have published in peer-reviewed literature or scientists with another qualification. Art.5 provides for 'scores' of candidates but again the criteria for 'scoring' are not disclosed[87]. Art. 6 includes a review procedure 'to ensure transparency', but we did not obtain information on the review of expert selection on our requests to EFSA. This could also not be found on EFSA's website[88] nor the names of these independent 'external reviewers', as selected by EFSA. In the case of the CEF/ANS panels[89] we noted that 6 criteria are applied, (i) experience in carrying out scientific risk assessment and/or providing scientific advice; (ii) proven scientific excellence; and (iii) experience in peer reviewing scientific work and publications, (iv) experience in analysing complex information and dossiers (v) experience in project management related to scientific matters; and (vi) experience in communication. All still very general to define a 'scientist' and leaving ample room for manoeuvre to include non-excellent scientists. Just as the case in this report (chapter 7) on the working group for the criteria for endocrine disruption demonstrates. Scientific excellence should in this case lead to experienced mammalian endocrinologist/clinician included in this working group, but this is not the case, only 3 out of 18 members are a mammalian endocrinologist/clinician, while the initial list (November 2012) had no mammalian endocrinologist/clinician on board at all. And 11 out of 18 have no experience whatsoever on endocrinology. The definition of EFSA's "scientist" remains a major issue, also in relation to the EU Food law that calls for "independent scientists".

This independence is still the major topic that should get attention in EFSA. It has been

known from the beginning in 2004 that EFSA has a big problem with conflicts of interest. This has led to numerous discussions in the European Parliament on the need to adopt a policy on conflicts of interest, that EFSA in the end reluctantly adopted in its regulations. In this report we noted elements of questionable independence of experts in EFSA's working groups, but - apart from the obvious cases - it remains difficult to conclude if a conflict of interest or a questionable independence leads to biased opinions. It very much looks like the 'conflict of interest' policy that the European Parliament imposed on EFSA in 2014[90], didn't change much in practice. Our report identifies still the same names of Benford, Schlatter, Van Benthem, Crebelli, Solecki in the 2018 (Ch. 5.5) while even industry employees or industry consultants are included as a member and in the 2019-Guideline (Ch. 6.5) working groups more familiar names like Benford, Schlatter, Gundert-Remy, Kleiner.

In this report we focussed on the content of the opinions and tried to analyse EFSA's opinions on genotoxicity (and the hazard approach in general) on science and ideology. The wide gap we observe between academic science and EFSA's regulatory science is obvious. For instance, the (widening) gap between regulatory experts, such as from EFSA, that consider that 'low dose' effects do not exist, that safe thresholds always exist for chemicals, also for genotoxic carcinogens, that favour a range of tools ('historical control data'[91], 'recovery of animals'[92], 'threshold of toxicological concern'[93], 'indirect effects', 'secondary effects' -see Ch. 5.5 of this report-, etc.) that disqualify adverse effects observed in test animals based on assumptions, and other experts, generally independent academics, that conclude, based on available scientific information, that 'low dose' effects are relevant, do question safe levels claimed without any experimental evidence and oppose the use of regulatory tools, again if not based on experimental evidence, to disqualify experimental test outcome. We tried to rank EFSA's opinion on genotoxicity (and the hazard approach) between the two extremes in Table 12.

TABLE 12. INDICATION OF IDEOLOGICAL POSITION OF THE DIFFERENT EFSA WG'S THAT HAVE BEEN ACTIVE ON GENOTOXICITY.

	EXPERIMENTAL RESULTS AS A BASIS, USING CURRENT SCIENTIFIC INSIGHTS	TRADITIONAL RISK ASSESSMENT; BASED ON EXPERIMENTAL RESULTS (SUBMITTED BY INDUSTRY) AND ON ASSUMPTIONS (EXPERT JUDGEMENT)	EXTENDING TRADITIONAL RISK ASSESSMENT WITH NEW ELEMENTS THAT LOWERS HUMAN PROTECTION AND EASE APPROVAL OF PESTICIDES	DEVIATING FROM EU POLICY/LAW THAT LOWERS HUMAN PROTECTION AND EASE APPROVAL OF PESTICIDES
EFSA 2005 on genotox (Ch 5.1.3)				
EFSA/ILSI 2005 on genotox and MOE (Ch 5.2)				
EFSA 2011 on genotox testing (Ch. 5.3)				
EFSA 2012 on MOE for impurities (Ch 5.4)				
EFSA 2015-2018 Standing Wg. on genotoxicity (Ch 5.5)				
EFSA 2010-2012 wg TTC for carcinogens (Ch 6.2)				
EFSA/ILSI partnership, 2011 (Ch 6.3)				
EFSA review 2014 (Ch. 6.4) and Guideline 2019 (Ch 6.5)				
EFSA 2013 wg. endocrine disruption (Ch 7.1)				

10. CONCLUSIONS

There is a big gap between EFSA's opinions on genotoxicity and the views of academic scientists and EFSA positions itself mainly on the side of easing the approval of pesticides and of the free market ideology

In our assessment in 0 out of the 9 cases studied, EFSA's opinion were in line with the current insights in science; this is worrying, since pesticide Regulation 1107/2009 requires that the assessment is done *"in the light of current scientific and technical knowledge"*(Art.4)

In our assessment 0 out of the 9 cases studied on genotoxicity and 'hazard approach' substances landed in the column "traditional risk assessment". This is surprising, since EFSA many times claims that risk assessment is the core of its work; for the genotoxic chemicals apparently EFSA concludes that risk assessment is not sufficient to get to a conclusion

In our assessment in 4 out of the 9 cases studied, EFSA's opinions landed in the column: "Extending traditional risk assessment with new elements that lowers human protection and ease approval of pesticides", mainly because of designing loopholes from the EU "no contact with humans" policy and lifting data requirements

In our assessment in 5 out of the 9 cases studied, EFSA's opinions ended up in the column: "Deviating from EU policy/law that lowers human protection and ease approval of pesticides", taking political decisions on allowing genotoxic metabolites and impurities on the market and undermining the hazard approach

Generally, the judgements by the EFSA wg. are one-sided, discussing 'false positives' (enhancing the approval of a pesticide), while 'false negatives' (possible leading to a ban of a pesticide) are disregarded; lifting test requirements because of "reducing animal testing" again eases market access of chemicals, while assuming that effects are "indirect" and can be disregarded (without experimental data to prove this effect) lead to the same outcome: less human health protection, more market access

Remarkably, most working groups on genotoxicity are an own initiative from the Scientific Committee, raising the question if (some members of the) EFSA panels are part of a specific advocacy group

EFSA does not manage (or does not choose) to get high-level academic scientists on board (genotox 2018, 4 out of 14; endocrine 6 out of 18 active scientists)

Many experts invited to a working group have not done experimental work in the field discussed (endocrine only 3 out of 18 members endocrinologists)

EFSA's selection criteria for experts more or less exclude independent scientists, causing experts with a regulatory background to dominate

The decisions in EFSA on the composition of working groups are a complete black box (EFSA claims that no documents are available)

The "hearing expert" practice of EFSA should be abandoned, since it generally offers a seat to an industry-linked expert or industry consultant

Two occasions where EFSA had a closed meeting with industry-funded group ILSI (2005, 2011) to draft opinions are in strong contradiction to its own claim that *"we should highlight that EFSA, due to its maximum commitment to the core values of transparency and independence, continually endeavours to further increase its engagement with civil society"*;

The story on TTC is nothing less that thinly covered lobby work, with the same core experts that designed TTC, the same that made its way to the EFSA panel and drafting EFSA's opinion on TTC, the same that organised a EFSA-ILSI TTC partnership meeting, and the same being the ones that have been performing an EFSA-WHO 'review' in 2014, where again all stakeholders except industry and ILSI not invited

We analysed EFSA's policy on selecting experts and its view on science in the past 15 years, and virtually nothing has changed, the majority of a working group still has a questionable independence; the policy on conflict of interest that EFSA had to adopt because of the European parliament, didn't change much, expert might have officially cut ties with industry, but many are the same people, with likely the same views

11. RECOMMENDATIONS

A full remake of EFSA's management, panels and working groups is needed to include more independent people and experts and more active scientists

EFSA shall revise its opinions and guidelines and base them on current scientific insights, to start with all opinions on genotoxins and endocrine disruptors;

EFSA shall make sure that every working group or panel is composed in majority of active scientists that have done experimental work on the topic of the working group;

EFSA shall put in place a revised 'conflict of interest' policy that effectively excludes experts that worked for industry or industry-funded groups, published with industry or attended their meetings, in the previous 10 years;

EFSA shall stop self-mandating to avoid the risk of pressure groups in its panels to define the agenda; mandating should be decided in an open, democratic way;

The 'hearing expert' policy shall be abandoned to avoid industry-consultants taking a seat in the working group;

EFSA shall never again have a partnership meeting with one interest group (ILSI) and embrace a full balanced stakeholder policy;

EFSA shall be totally transparent on selection of experts in its panels and working groups, and publish all documents on the selection;

The 'Court of Auditors' and the European parliament are encouraged to perform an audit on the question if EFSA is following its mission in its opinions published and uses its money in a correct way or is part a certain Thought School and misuses public money.

ANNEX I.

LOW DOSE COLLECTION

In the regulatory arena, decisions are almost entirely made based on industry-sponsored studies that are generally carried out according to OECD-protocols and done by Good Laboratory Practices (GLP) laboratories. These safety test studies are performed at high unrealistic doses to limit test animals and reduce costs for industry. The data on low dose realistic effects of chemicals in the regulatory arena are scarce and almost absent. Independent (academic) scientists do publish data on low dose effects of chemicals, at least more than in industry-sponsored studies. Below, a range of data from studies in (peer-reviewed) scientific journals are collected.

CHEMICAL (ENDOCRINE DISRUPTOR)	INDEPENDENT STUDIES NOEL/LOEL[94] (FINDINGS IN G/KG BW., PPB) CF. TTC NOEL CUT-OFF LEVEL OF 150 G/KG BW. FOR 'CRAMER III'.
Bisphenol A	2 (LOEL, mice)[95]
Fenarimol	2 (LOEL, mice)[96]
DES	0,02 (LOEL, mice)[97]
Atrazin	1 (LOEL, mice)[98]
PBDE-99	60 (LOEL, rats)[99]
Fipronil	100 (LOEL, rats)[100]
Nonylphenol	100 (LOEL,rats)[101]
Terbuthylazine	4 (LOEL, rats)[102]
Di-n-butyl phthalate	10 (LOEL, rats)[103]
Hexachlorobenzene + 123-trichlorobenzene	0,1 (LOEL, rats)[104]
BDE-47	2 (LOEL, rats)[105] 0,2 (LOEL, lambs)[106]
Chlorpyrifos	10 (LOEL, rats)[107]
Perchlorate	10 (LOEL, rats) [108]
Methoxychlor	20 (LOEL, mice)[109]
Octylphenol	10 (LOEL, pigs)[110]
Deltamethrin	3 (LOEL, rats) [111]
0,p'-DDT	18 (LOEL, mice)[112]
PFOA	10 (LOEL, mice)[113]
Ethinylestradiol	0,2 (LOEL, rats)[114]
L-cyhalothrin	200 (LOEL, mice)[115]
Triflumizole	8,6 (LOEL, mice)[116]
TBT	O,53 (LOEL, mice) [117]
DHEP	15 (NOEL, rats)[118]
Dieldrin	5 (NOEL)[119]
Haloxyfop Methyl	5 (NOEL)[120]

FOOTNOTES

by clicking the footnote's number you can jump back to the referred text page

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8. Reg 178/2002, whereas 46: "In order to guarantee independence, members of the Scientific Committee and Panels should be independent scientists recruited on the basis of an open application procedure".
9. Whereas 18: In order for there to be confidence in the scientific basis for food law, risk assessments should be undertaken in an independent, objective and transparent manner, on the basis of the available scientific information and data
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18. Sabine A.S.Langie et al., Causes of genome instability: the effect of low dose chemical exposures in modern society, Carcinogenesis, 2015, Vol. 36, Supplement 1, S61–S88
19. J. O'Brien, A.G. Renwick, A. Constable, E. Dybing, D.J.G. Muller, J. Schlatter, W. Slob, W. Tueting, J. van Benthem, G.M. Williams, A. Wolfreys, Approaches to the risk assessment of genotoxic carcinogens, Food and Chemical Toxicology 44 (2006) 1613–1635
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21. Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic, The EFSA Journal (2005) 282, 1-31
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31. This is how ILSI/IVGT would like to be considered: "The Emerging Issues Subcommittee of the ILSI Health and Environmental Sciences Institute (HESI) started the Relevance and Follow-up of Positive Results from In Vitro Genetic Toxicity Testing (IVGT) project in June 2006. The aim of the ILSI/HESI is to stimulate and support scientific research and educational programs that contribute to the identification and resolution of health and environmental issues of concern to the public, scientific community, government agencies, and industry. HESI's scientific programs bring together scientists from around the world from academia, industry, and regulatory agencies and other governmental institutions, to address and reach consensus on scientific questions that have the potential to be resolved through creative application of intellectual and financial resources. As a non-profit organization, HESI provides a unique, objective forum for initiating dialogue among scientists with different perspectives and expertise".

32. Quote EFSA opinion: "During the last years, the non-thresholded mechanism of DNA-reactive chemicals has been questioned, at first on a theoretical basis, taking into account the presence of cellular defence mechanism (scavenging, detoxification, DNA repair etc.) that can protect DNA at low exposure levels".

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46. PAN Europe report Toxic mixture

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