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ARTICLE

Reasons for Reinforcing the Regulation of Chemicals in Europe

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Abstract

The European Commission's 2020 draft Chemicals Strategy for Sustainability set the ambitious goal of achieving a "Toxic-Free Environment". Those ambitions were harshly criticised by a team based in Germany's Federal Institute for Risk Assessment (or BfR); they claimed that toxicological risks from chemicals had already been minimised and were optimally regulated. This paper outlines evidence to support the Commission's implication that the European Union's chemicals regulatory regime is sub-optimal. It also criticises the BfR team's contentions by reference to empirical findings (eg concerning tumours, congenital anomalies and the toxicity of mixtures) and by disentangling their conceptual confusions.

Keywords: Chemicals Strategy; European Commission; pesticides; sustainability

I. Introduction: the policy context

The European Commission's October 2020 draft Chemicals Strategy for Sustainability (CSS) was an ambitious document; it was subtitled "Towards a Toxic-Free Environment". In its introduction, the draft CSS correctly stated that the European Union (EU) "already has one of the most comprehensive and protective regulatory frameworks for chemicals",[1] yet it aspired to create a toxic-free environment. While the EU's standards are amongst the highest, when compared with other jurisdictions, the Commission implicitly acknowledged that the EU's standards could and should be higher. While it is true that the EU's standards are often relatively high, the implementation of the EU's regimes in practice remains problematic. The CSS aspires fully to "protect environment and human health, in particular that of vulnerable groups".

Nonetheless, some commentators criticised the Commission's CSS as unnecessary. In particular, senior members of the German government's Federal Institute for Risk Assessment (the Bundesinstitut für Risikobewertung or BfR) have argued that

> the implementation of a complex and interdependent network of regulations for chemical substances, including industrial chemicals, plant protection products, biocides, or chemicals in food and feed has *minimised* toxicological risks and has

[1] European Commission, "Chemicals Strategy for Sustainability Towards a Toxic-Free Environment" COM(2020) 667 final <https://eur-lex.europa.eu/resource.html?uri=cellar:f815479a-0f01-11eb-bc07-01aa75ed71a1.0003.02/DOC_1&format=PDF>.

> continuously increased public health and wellbeing in the EU. Moreover, although *this framework already provides one of the most advanced regulatory systems worldwide, it is constantly pressed for improvement … the respective regulatory processes are optimised with respect to both their efficiency and effectiveness.*[2] (emphasis added)

The BfR team argued that EU regulations of chemical risks are already optimal, so there is no scope – and hence no need – for any significant tightening of the prevailing regime. The BfR team judged the status quo to be entirely acceptable.

The CSS envisaged attaining its goal by incentivising the replacement of unsafe chemicals with others that will be "safe by design"; it envisaged a completely fresh trajectory for chemicals research, development and innovation. The CSS argued: "*Novel and cleaner industrial processes and technologies* would help not only to lower the environmental footprint of chemicals production but also to reduce costs, improve market readiness and create new markets for the European sustainable chemicals industry" (p 7, emphasis in the original). We applaud the CSS's ambitions, and this paper provides a critique of the BfR team's objections to the CSS and orthodox defences of the status quo.

II. Our perspective and framing assumptions

Before advancing our critique, several preliminaries should be made explicit. This paper is predicated on key well-grounded assumptions about the characteristics of the issues under discussion. The topic is located at the intersection of science and policymaking. Whenever expert advisory bodies provide "risk assessments" to policymakers, both scientific and policy considerations are unavoidably involved and interconnected in important ways. Examples are provided below. Nonetheless, the influences of both sets of considerations and their interactions are often not explicitly acknowledged. While many scientific advisory bodies and the policymakers they advise claim that their judgments are based on – and only on – scientific considerations, this is almost always misleading. As academic philosophers frequently observe: you cannot derive an "ought" from an "is".

If scientific advice to policymakers was entirely derived just from scientific considerations, it should always take a plural and conditional form rather than a monolithic and prescriptive form.[3] For example, it could indicate what is known and not known about the consequences of following – or failing to follow – a range of possible policy options that policymakers have enumerated. If, on the other hand, the advice recommends one particular course of action (eg "adopt and implement these measures"), value judgments must have influenced and contributed to that advice, even if those value judgments remain implicit and unacknowledged.[4]

Deciding, for example, what does and does not count as a relevant risk, which types of evidence are to be deemed relevant and how much of which types of evidence are deemed variously necessary and/or sufficient to sustain judgments in favour of accepting, restricting or banning some product or process all presuppose or imply value judgments; they are not empirical findings. Similarly, how the reliability of evidence of various sorts of studies is characterised and adjudicated depends on socially contestable value judgments. Those value judgments are increasingly – and informatively – coming to be termed "risk assessment policy" judgments.[5]

[2] M Herzler et al, "The 'EU Chemicals Strategy for Sustainability' Questions Regulatory Toxicology as We Know It: Is It All Rooted in Sound Scientific Evidence?" (2021) 95 Archives of Toxicology 2589.

[3] A Stirling, "'Opening Up' and 'Closing Down': Power, Participation, and Pluralism in the Social Appraisal of Technology" (2008) 33 Science, Technology, and Human Values 262.

[4] E Millstone, "Can Food Safety Policy-Making Be Both Scientifically and Democratically Legitimated? If So, How?" (2007) 20 Journal of Agricultural and Environmental Ethics 483.

[5] ibid.

The approach adopted in this paper will, therefore, involve making our own key value judgments explicit and indicating how they contribute to our understanding and interpretation of the science and to our policy judgments and recommendations. We shall, moreover, also endeavour to make explicit some of the value judgments that have been implicit in the advice and conclusions of the institutions that we shall be discussing, in particular the European Commission and its CSS and the BfR.

Chemical risk assessment policy decision-making operates in a contestable and often contested space because different groups of stakeholders have different and often conflicting interests. Firms that manufacture, sell and use chemicals have commercial interests that depend on, for example, national governments and the European Commission categorising their compounds as acceptably safe for sale and use. If, however, those products do or might pose risks to, for example, consumers, third parties or the natural environment, then the organisations focused on protecting public and environmental health often favour tight restrictions or even bans on the production, sale and use of those materials.

Biomedical sciences in general – and toxicology in particular – often have to deal with biological variability within and between species and populations, and therefore they often can provide only estimates of probabilities rather than certainty or precision. This is evident, for example, whenever official bodies chose to use a "weight of evidence approach". Such decisions inevitably reflect contestable value judgments when assigning the "weights". In practice, when official bodies claim to have applied a "weight of evidence" approach, it has often involved assigning weights to different pieces of evidence in ways that were neither consistent (as, for example, between putative false positives and putative false negatives) nor transparent or justified.[6]

Whenever risk assessors provide advice to risk managers that recommends one particular course of action, those recommendations invariably presuppose some value judgments, which provoke questions concerning whether those judgments favour the protection of public and environmental health or the interests of commercial organisations. Our values presume prioritising the protection of public and environmental health over commercial interests, or even over seeking to balance equally between those two conflicting interests. Those values inform our analysis and assessment of the status quo, which we judge to be inadequate, and consequently we interpret the CSS as a welcome step in the right direction.

III. The scientific case for the Commission's Chemical Strategy for Sustainability

Herzler et al criticised the CSS by arguing that "without a detailed assessment of which risks are currently deemed to be insufficiently addressed, it is hard to establish whether additional regulation might be necessary or existing regulation might need to be improved, and for which part of the population".[7] But that approximates to arguing that, until a quantitative risk assessment has been completed, it would be premature to regulate on the basis of partial incomplete information, which implies that precaution should never be exercised. While the CSS did not provide a detailed assessment of the hazards or risks that it highlighted, it did not claim that it would or had. The CSS did not purport to provide a purely scientific argument for the directional policy shift that it was proposing. The CSS

[6] P Clausing, C Robinson and H Burtscher-Schaden, "Pesticides and Public Health: An Analysis of the Regulatory Approach to Assessing the Carcinogenicity of Glyphosate in the European Union" (2018) 72 Journal of Epidemiology and Community Health 668; E Millstone and E Dawson, "EFSA's Toxicological Assessment of Aspartame: Was It Even-Handedly Trying to Identify Possible Unreliable Positives and Unreliable Negatives?" (2019) 77 Archives of Public Health 34.

[7] Herzler et al, supra, note 2.

drew attention to the limitations of the available science; it complained about what it referred to politely as "data gaps" concerning, for example, levels of exposure and under-examined toxicological endpoints. The CSS was making a value judgment about the policy implications of such data gaps and scientific uncertainties. The approach adopted in the CSS is entirely consistent with Regulation (EC) No 1107/2009 that covers pesticidal products, which states: "The precautionary principle should be applied and this Regulation should ensure that industry demonstrates that substances or products produced or placed on the market do not have any harmful effect on human or animal health or any unacceptable effects on the environment."[8]

There are, moreover, extensive bodies of robust evidence indicating that the prevailing chemicals regulatory regime is not sufficiently protective of public health. The same is almost certainly true for the health of ecosystems, but this paper only focuses on threats to public health. An exhaustive review of the different types of harm that chemicals may be causing is beyond the scope of this paper, but several clear examples should be sufficient.

1. Carcinogens are inadequately regulated

In relation to cancer, there is extensive evidence that fatalities due to cancer have steadily diminished, but that information falls far short of providing a complete picture. It ignores the fact that the incidence of several types of commonly occurring cancers have been rising steadily since, for example, the 1970s. Herzler et al highlighted the fact that "life expectancy and healthy life years ... while varying between EU Member States, have been rising more or less constantly for many years".[9] But while cancer mortality rates have fallen, this has been because of improved early detection of tumours and gains in therapeutic efficacy rather than because of official regulatory measures. If the regulatory measures were sufficient, incidences would have fallen, not risen.

The occurrence and diagnosis of primary tumours, even in patients who survive, inflict immense sorrow, anxiety and costs on individuals and their families, as well as impacting health systems and economies. The long-run increases in the incidence of cases of many common types of cancers show that prevailing regulatory regimes are not just suboptimal but seriously inadequate. For example, in 2015, Haberland and Wolf reported a continuous increase in the age-corrected incidences of breast cancer (2.2-fold) and prostate cancer (2.7-fold) in Germany between 1970 and 2010.[10] They also reported a modest decline in fatality rates of those two types of cancer.

In the UK, similar patterns have occurred. Cancer Research UK (CRUK) gathers and analyses relevant data and publishes tables and graphic representations of those data on its website.[11] CRUK provides, for example, graphics showing the "20 Most Common Cancers" in both women and men and indicating "Percentage Changes in Age-Standardised Three Year Average Incidence Rates, UK, 2006–2008 and 2016–2018". They clearly show that the incidence rates of many types of tumours have been rising rather than falling. Similar patterns have emerged in many other jurisdictions.

[8] European Parliament and Council, "Regulation (EC) No 1107/2009 of 21 October 2009 Concerning the Placing of Plant Protection Products on the Market and Repealing Council Directives 79/117/EEC and 91/414/EEC" (2009) Official Journal of the European Union 1 <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32009R1107>.

[9] Herzler et al, supra, note 2.

[10] J Haberland and U Wolf, "Trendanalysen zur Inzidenz und Mortalität an Krebs in Deutschland seit 1970" (2015) 11 GMS Medizinische Informatik, Biometrie und Epidemiologie Doc03.

[11] Cancer Research UK, "Cancer incidence for common cancers" <https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Three>.

Table 1. Prevalence of congenital anomalies per 10,000 births (five-year arithmetic means) in the European Union for the periods 1980–1984 and 2015–2019 for selected groups of anomalies.

Anomalies	1980–1984	2015–2019	Increase
All anomalies	210	258	×1.2
Congenital heart defects	46.9	81.1	×1.7
Respiratory anomalies	1.66	4.16	×2.5
Abdominal wall defects	3.31	4.57	×1.4
Genital anomalies	15.5	20.2	×1.3

Note: We report five-year arithmetic means as indicators of prevailing trends.
Source: <https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en>, where more details can be found.

2. *Endocrinological and reproductive toxicity remains insufficiently controlled*

In relation to reproductive toxicology, Herzler et al implied that the status quo was unproblematic because "the prevalence of anomalies in the newborn in the EU has been practically constant (at around 200/10,000) for the past 40 years", although they acknowledged that they did not include genetic anomalies or adjust for parental age.[12] An examination of the database used by Herzler et al shows that their statement was misleading; the evidence for this claim is provided in Table 1.

Firstly, the prevalence of all anomalies in new-borns in the EU has not been "practically constant". On the contrary, it has increased slowly but continuously, with a 20% increase for the period of 2015–2019 (last year available) compared to 1980–1984. The data show even greater increases for four specific types of anomalies, although some declined over that interval. The reasons for those changes need to be elucidated, but the overall prevalence increased rather than remaining practically constant.

Furthermore, a major health concern with regard to reproductive toxicity has been – and remains – diminishing fertility rather than birth defects. In 1992, Carlsen et al published evidence showing that, in Europe, adult male sperm counts had fallen by approximately 50% in 50 years.[13] Skakkebaek et al recently reported a severe worldwide decline in fertility over the previous five decades. According to the authors, it remains to be elucidated whether this decline is due to exposure to environmental contaminants, changes in lifestyles or both, but increasing incidences of testicular cancer are widely considered to be a result of environmental exposures to contaminants.[14] Furthermore, Levine et al conducted a meta-analysis of the results of 223 such studies and reported that sperm counts have been declining on all continents and that these rates of decline have accelerated.[15]

A report commissioned by the World Health Organization (WHO) and the United Nations Environment Programme (UNEP) articulated serious concerns about the rising incidence of many endocrine-related diseases and disorders and the widespread detection of endocrine-disrupting compounds (EDCs), as well as "significant uncertainties about the true extent of

[12] Herzler et al, supra, note 2.

[13] E Carlsen et al, "Evidence for Decreasing Quality of Semen During Past 50 Years" (1992) 305 British Medical Journal 609.

[14] NE Skakkebaek et al, "Environmental Factors in Declining Human Fertility" (2022) 18 Nature Reviews Endocrinology 139; see also JJ Meeks, "Environmental Toxicology of Testicular Cancer" (2012) 30 Urologic Oncology 212; L de Toni, "Testicular Cancer: Genes, Environment, Hormones" (2019) 10 Frontiers of Endocrinology 408.

[15] H Levine et al, "Temporal Trends in Sperm Count: A Systematic Review and Meta-Regression Analysis of Samples Collected Globally in the 20th and 21st Centuries" (2022) Human Reproduction Update dmac035 <https://doi.org/10.1093/humupd/dmac035>.

risks from chemicals" due to the lack of data.[16] It is sensible to assume that those problems have not diminished during the nine years that it took the European Commission to set out its "scientific criteria for the determination of endocrine disrupting properties".[17]

The EU's process of classifying particular compounds as EDCs and banning them only started recently, and only a very few chemicals have so far been banned, despite evidence that approximately 800 chemicals are known or suspected EDCs. Two studies that employed extensive Monte Carlo simulations estimated that health costs in the EU due to EDCs exceed 150 billion euros annually.[18]

3. Toxicity of combination effects from chemical mixtures

Herzler et al provided a discussion of possible combination effects (ie the possibility of additive or even synergistic adverse effects of multiple exposures to chemicals). Their narrative implied, however, that everything that might deserve to be done was already being done because – according to them – "intentional/foreseeable mixtures are already explicitly addressed in some of the EU's major regulatory programs (e.g. pesticides and biocides)".[19]

"Addressed" is not a particularly precise term. While the European Food Safety Authority (EFSA) has issued a Guidance Document on this matter,[20] its practical application has so far been limited to additive effects from oral exposures of suspected pesticidal compounds on two endpoints, namely acute effects on the nervous system[21] and chronic effects on the thyroid.[22] Moreover, combination effects under different routes of exposure (eg by inhalation and/or dermal in addition to oral) and chemicals other than pesticides/biocides have not yet been included.

Moreover, the toxicological database is incomplete and often equivocal, and its reliability is problematic. Our knowledge of the scope and limits of the validity of extrapolative inferences from animal studies to human risks is insufficient. Available concordance analyses of newly developed pharmaceutical drugs offer promising opportunities for enriching the scientific basis of policymaking. In contrast to pesticides and industrial chemicals, candidate pharmaceuticals, if reassuring data from animal studies are available, are deliberately given to people, and both animals and patients are carefully monitored. According to Clarke and Steger-Hartmann, the concordances between animal and human studies vary between more than 70% and less than 30%, depending on the organ system.[23] More importantly, "absence of toxicity in animals has very low predictivity for the lack of adverse

[16] A Bergman et al, "State of the Science of Endocrine Disrupting Chemicals 2012" (United Nations Environment Programme and the World Health Organization, 2013) <https://www.unep.org/resources/report/state-science-endocrine-disrupting-chemicals>.

[17] Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0605&from=EN>.

[18] L Trasande et al, "Estimating Burden and Disease Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union" (2015) 100 Journal of Clinical Endocrinology & Metabolism 1245; L Trasande et al, "Burden of Disease and Costs of Exposure to Endocrine Disrupting Chemicals in the European Union: An Updated Analysis" (2016) 4 Andrology 565.

[19] Herzler et al, supra, note 2.

[20] EFSA, "Guidance Document on Scientific Criteria for Grouping Chemicals into Assessment Groups for Human Risk Assessment of Combined Exposure to Multiple Chemicals" (2021) 19 EFSA Journal 7033.

[21] EFSA, "Cumulative Dietary Risk Characterisation of Pesticides That Have Acute Effects on the Nervous System" (2020) 18 EFSA Journal 6087.

[22] EFSA, "Cumulative Dietary Risk Characterisation of Pesticides That Have Chronic Effects on the Thyroid" (2020) 18 EFSA Journal 6088.

[23] M Clarke and T Steger-Hartmann, "A Big Data Approach to the Concordance of the Toxicity of Pharmaceuticals in Animals and Humans" (2018) 96 Regulatory Toxicology and Pharmacology 94.

events in humans".[24] Such evidence of uncertainty from human drug studies represents a profound challenge to Herzler et al's complacency, especially regarding mixtures. That challenge is amplified by the findings of a recent systematic review of 1,220 studies of mixtures, which emphasised that two-thirds of the studies were solely based on mixtures of just two compounds and that "toxicity outcomes of relevance for human risk assessment (e.g. carcinogenicity, genotoxicity, reproductive toxicity, immunotoxicity, neurotoxicity) were rarely addressed".[25]

IV. Herzler et al's perspective versus precaution

While Herzler et al's concern that "the strong push" of the CSS for a stricter regulation of chemical mixtures "is not sufficiently data driven", our interpretation is that the BfR team's position is antithetical to the EU's precautionary legislation. The precautionary principle is supposed to be used in case of scientific uncertainty[26]; the legislation mandates the introduction and/or maintenance of regulatory measures in the absence of *demonstrated risks*. Herzler et al simply misunderstand precaution.

The BfR team implies that the reality of risk needs to be proven before any measures can be justified and that evidence that falls short of demonstrable proof should never be sufficient, except perhaps for carcinogenic, mutagenic or reprotoxic substances (CMRs) or EDCs. Firstly, that is self-evidently a value judgment, not an empirical finding, but no less importantly it is a value judgment that implies consistently awarding the benefits of all and any uncertainties to the commercial interests of the companies that produce, trade in and use the chemicals in question rather than to the protection of, for example, occupational, public and environmental health.

Herzler at al accepted that "precaution" could be appropriate in relation to CMRs or EDCs, but only if those measures are "proportional". But Herzler et al assume that measures should always be proportional to the magnitudes of particular risks. However, if the magnitudes of the possible risks are uncertain, then the requirement for proportionality cannot be satisfied.

The arguments outlined and the evidence adduced in this section therefore support the European Commission's judgment that the prevailing chemical regulatory regime may not sufficiently protect public health, and consequently that it could – and should – be strengthened.

V. The Chemical Strategy for Sustainability's strategy and tactics

To attain the strategic objectives on which the CSS focused, the Commission proposed several tactical reforms, although some of them were under-described. One important change of tactics is the proposal to broaden the scope of EU chemical risk assessments to include wider ranges of potential impacts and outcomes than those currently included. That tactical change could be – and should be – acknowledged as a proposed change to a key EU risk assessment policy.

The plan to widen the scope of risk assessments was evident when, for example, the CSS recommended developing "methodologies for chemical risk assessment that take into account the whole life cycle of substances, materials and products" rather than merely assessing the safety of the particular use for which it will be sold. While the CSS

[24] ibid.

[25] O Martin, "Ten Years of Research on Synergisms and Antagonisms in Chemical Mixtures: A Systematic Review and Quantitative Reappraisal of Mixture Studies" (2021) 146 Environment International Article 106206.

[26] European Parliament and Council, supra, note 8.

optimistically implied that the prevailing regime was already doing a good job in relation to "chemicals that cause cancers, gene mutations, affect the reproductive or the endocrine system, or are persistent and bioaccumulative", it envisaged extending that "to further chemicals, including those affecting the immune, neurological or respiratory systems and chemicals toxic to a specific organ".[27] The CSS aspired to reduce morbidity as well as premature mortality. The CSS anticipated the EU's chemicals regulatory regime becoming more precautionary than the prevailing regime, although the word "precaution" appeared nowhere in the document.

The second tactical change focused in particular on EDCs, which interfere with hormonal systems. The CSS said that EDCs "require specific attention". The CSS proposed[28] to:

- ... establish *legally binding hazard identification* of endocrine disruptors ... building on criteria already developed for pesticides and biocides, and apply it across all legislation;
- ensure that *endocrine disruptors are banned in consumer products* as soon as they are identified, allowing their use only where it is proven to be essential for society;
- strengthen *workers' protection* by introducing endocrine disruptors as a category of substances of very high concern under REACH [the Registration, Evaluation, Authorisation and Restriction of Chemicals];
- ensure that sufficient and appropriate *information is made available to authorities* to allow the identification of endocrine disruptors by reviewing and strengthening information requirements across legislation;
- accelerate the development and uptake of *methods to generate information* on endocrine disruptors through screening and testing of substances. (emphases in the original)

That wording acknowledged that prevailing definitions of endocrine-disrupting hazardous chemicals had not been legally binding and had been applied unevenly, and that, even when such disruptors had been identified, they had often not promptly been banned. That is one reason why the CSS also called specifically for the "*full implementation* of the EU rules on chemicals" (emphasis in the original).[29] It also implicitly accepted that occupational risks from endocrine disrupters have not been adequately regulated, and that far too little information was available to EU authorities on the composition and toxicology of putative endocrine disrupters. This was partly because too few sufficiently sensitive and specific endocrinological studies have been conducted, but also because the Commission suspected that industry may have withheld some or all of the data they have regarding some of the studies that have been conducted. This is why the CSS explicitly articulated a new policy of: "ZERO TOLERANCE FOR NON-COMPLIANCE" (Section 2.3.2, p 18, emphasis in the original). It will "strengthen the principles of 'no data, no market' and the 'polluter-pays'" (ibid).

A third tactical change responded to the scale of the scarcity and inadequacies of the data. The CSS stated that the Commission will "amend ... information requirements to enable *identification of all carcinogenic substances* manufactured or imported in the EU" (Section 2.4.1, p 20, emphasis in the original), and that

> there is much knowledge to be acquired by authorities on the intrinsic properties of a vast majority of chemicals .... Equally, knowledge on uses and exposure is fragmented ... as it relies on industry to provide accurate information. The sheer

[27] European Commission, supra, note 1.
[28] ibid.
[29] ibid.

> number of chemicals on the market represents an immense knowledge challenge, and the expected future rise in chemical production and use risks further widening the "unknown territory of chemical risks". (Section 2.4, p 19)

The fourth proposed tactical change responded to the fact that EU regulatory bodies have often relied mainly on studies designed and conducted by or on behalf of the chemical industry, and that too little attention had been paid to studies conducted independently of corporate interests, as the CSS rather coyly observed that "*academic studies* are not sufficiently exploited" (Section 2.3.1, p 16, emphasis in the original).

The fifth proposed tactical change responded to the fact that, in relation to pharmaceutical products, pesticides and food ingredients, EU rules have recently been amended to stipulate that no study can be used in support of an application for market authorisation unless the protocol for that study had been notified to the Commission before the study commenced.[30] This is designed to ensure that companies no longer have the discretion to decide – for themselves and confidentially – whether or not to provide the EU's regulatory institutions with all data from all studies.

The sixth proposed tactical change focused on additional risks potentially arising from the combination effects of chemicals. It stated:

> People and other living organisms are daily exposed to a *wide mix of chemicals originating from various sources*. Significant progress has been made in recent years to close some knowledge gaps on the impact of the combination effect of those chemicals. However, the safety of chemicals in the EU is usually assessed through the evaluation of single substances, or in some cases of mixtures intentionally added for particular uses, without considering the combined exposure to multiple chemicals from different sources and over time .... Explicit requirements to take into account the impact of *unintentional mixtures* is generally lacking .... To adequately address the combination effect of chemical mixtures, legal requirements need to be consistently in place to ensure that risks from simultaneous exposure to multiple chemicals are effectively and systematically taken into account across chemicals-related policy areas ... scientific consensus is emerging that the effect of chemical *mixtures needs to be taken into account and integrated more generally into chemical risk assessments*. (Section 2.2.2, p 12, emphases in the original)

The seventh proposed tactical reform is to strengthen the regime covering chemical pollutants in the natural environment, so that environmental health as well as public health are properly protected. The CSS provided particular comments on one type of pollutant, namely the per- and poly-fluoroalkyl substances (PFASs)[31], which it said

> require special attention, considering the large number of cases of contamination of soil and water – including drinking water – in the EU and globally, the number of people affected with a full spectrum of illnesses and the related societal and economic costs. That is why the Commission proposes a comprehensive set of actions to *address the use of and contamination with PFAS*. (Section 2.2.3, p 13, emphasis in the original)

Overall, the CSS recognised many of the achievements of the EU's chemicals regulatory regimes, but also many of its limitations and shortcomings, and consequently it

[30] "Decision Laying Down the Practical Arrangements on Pre-Submission Phase and Public Consultations" (EFSA, 11 January 2021) <https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/210111-PAs-pre-submission-phase-and-public-consultations.pdf>.

[31] See, eg, <https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas>.

highlighted at least seven key respects in which the Commission judged that those regimes could and should be strengthened, not just in the sense of being more restrictive, but also in the sense of being more comprehensive, better informed and more accountable by being more transparent.

VI. The BfR team's response to the CSS

Herzler et al's critical response to the CSS provided a complacent narrative, asserting that toxicological risks from chemicals had already been minimised and that the prevailing regulatory regimes had been "optimised".[32] It implicitly assumed that all toxicological risks have been exhaustively identified, documented, quantified and subjected to controls that are comprehensive, effective and sufficient. That judgment combined both factual and normative considerations, many of which we do not share and are contesting.

The BfR team argued that, while there might be a role for the Commission to consult with a broad range of social, environmental and commercial stakeholders, decisions about the composition and implementation of a chemicals sustainability strategy should be taken only by reference to scientific considerations. We reiterate, however, that science alone can never settle policy questions. The BfR team implied that its own narrative was an entirely scientific one; we shall, however, provide evidence showing that it was replete with unacknowledged value judgments.

The BfR team asserted that

> institutions, like the German Federal Institute for Risk Assessment (BfR), have a decade-long record of both practically applying and further developing the principles and methods of the science of regulatory risk assessment for consumer health protection in the EU ... it is one of their foremost tasks to safeguard that scientific rigour is applied as the cornerstone of chemical risk assessment ...[33]

VII. A critique of Herzler et al and of the status quo

The above is a surprisingly bold assertion from the BfR given its profoundly flawed approach to producing a risk assessment of the controversial herbicide glyphosate. One would at least have expected that all applicable regulations and guidelines had been properly followed by the BfR when it prepared for the EFSA and the European Commission its draft Renewal Assessment Report (RAR) of glyphosate in 2015. However, several flaws remained in the BfR's RAR, though some of these were corrected in an Addendum,[34] which rapidly emerged at the end of August 2015 in response to the International Agency for Research on Cancer (IARC) monograph on glyphosate that had been published a few weeks earlier. Other flaws in the BfR's RAR, however, remained unaddressed.

One of the flaws that was corrected was a reassessment of statistical significances using a proper statistical procedure. In the Addendum, BfR acknowledged that "initially, the RMS [Rapporteur Member State] [had] relied on the statistical evaluation provided with the study reports".[35] That wording reveals that the BfR failed to conduct an independent statistical assessment of the data provided by the industry's Glyphosate Taskforce until after

[32] Herzler et al, supra, note 2.

[33] ibid, page 2590.

[34] Rapporteur Member State (RMS) Germany, "Glyphosate. Addendum 1 to RAR: Assessment of IARC Monographs Volume 112 (2015): Glyphosate".

[35] ibid.

it came under political pressure, once IARC asserted that glyphosate is "probably carcinogenic to humans".[36] Only then did the BfR conduct its own statistical evaluation, which used a statistical method appropriate for evaluating tumour incidences, namely a trend test, rather than the pairwise comparisons that were reported in Glyphosate Taskforce documents.

The BfR also initially ignored available evidence of glyphosate exposure causing oxidative stress, which is a potentially relevant mechanism that could explain the development of tumours. That evidence had not been acknowledged in its original assessment. Only after IARC had identified "strong evidence that glyphosate ... can act to induce oxidative stress"[37] did the BfR acknowledge this in the RAR Addendum.

Both the BfR and subsequently EFSA discounted evidence of glyphosate's carcinogenicity by claiming that the dose levels used in some of the mouse studies exceeded what they alleged was a maximum "limit dose" of 1,000 mg/kg.[38] But no such limit has been officially specified for carcinogenicity studies. The Organisation for Economic Co-operation and Development (OECD) guidance documents, to which the RAR referred, had recommended a maximum dose of 1,000 mg/kg for chronic toxicity studies but not for carcinogenicity studies.[39] The spurious tactic of citing the OECD was invoked by the BfR in its 2015 report on glyphosate, by EFSA in its conclusions on glyphosate, in the Harmonised Classification and Labelling (CLH) report on glyphosate and again in a recent draft report on glyphosate of the EU's Assessment Group on Glyphosate,[40] even after the limit-dose argument had repeatedly been criticised in peer-reviewed journals.[41]

Instead, OECD guidance document No. 116 recommended avoiding dietary concentrations of test substances higher than 50,000 mg/kg in long-term bioassays.[42] This concentration is well above the highest concentrations of 20,000 and 30,000 mg/kg used in two of the mouse carcinogenicity studies on glyphosate. This was, however, never acknowledged by the BfR, EFSA or the European Chemicals Agency (ECHA).

VIII. Further problems with the status quo

Another problematic feature of the status quo in official EU toxicological assessments of the carcinogenic potential of pesticides has been the tactic of invoking historical control data (HCD) as grounds for discounting evidence of adverse effects, especially increased tumour incidences. Often when corporate interests want to discount putative evidence of toxicity that emerges from comparing evidence of adverse effects in groups of test animals with evidence from the concurrent control group, they argue that the tumour incidences seen in the concurrent control group were unusually low when compared to

[36] International Agency for Research on Cancer (IARC), "Some Organophosphate Insecticides and Herbicides" (2017) 112 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.

[37] ibid.

[38] RMS Germany, "Renewal Assessment Report Glyphosate" (2015) Volume 3 Annex B.6. Toxicology and Metabolism; EFSA, "Conclusion on the Peer Review of the Pesticide Risk Assessment of the Active Substance Glyphosate" (2015) 13 EFSA Journal 4302.

[39] Organisation for Economic Co-operation and Development (OECD), "Guidance document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Test Guidelines 451, 452 and 453, 2nd Edition" (2012) 116 Series on Testing and Assessment; OECD, "Combined Chronic Toxicity/Carcinogenicity Studies" (2009) 453 Guideline for the Testing of Chemicals.

[40] RMS Germany, supra, note 38; EFSA, supra, note 38; Assessment Group on Glyphosate, "Combined Draft Renewal Assessment Report and CLH Report. Glyphosate" (2021) Volume 1.

[41] CJ Portier and P Clausing, "Re: Tarazona et al. (2017): Glyphosate Toxicity and Carcinogenicity: A Review of the Scientific Basis of the European Union Assessment and Its Differences with IARC" (2017) 91 Archives of Toxicology 3195; Clausing et al, supra, note 6.

[42] Organisation for Economic Co-operation and Development (OECD), supra, note 37.

control groups examined previously in earlier studies. They argue that if the test animals were compared to historical control groups the differences would cease to be statistically and/or toxicologically significant.

OECD guidance document No. 116[43] and Guidance of the European Chemicals Agency[44] both provided very similar recommendations for the conditions under which HCD can legitimately be used to interpret new data. While HCD on tumour incidences in earlier control groups may sometimes be relevant when assessing the findings of recent studies, OECD emphasised "that the concurrent control group is always the most important consideration in the testing for increased tumour rates".[45] Similarly, ECHA stipulated that "historical data must be from the same animal strain/species, and ideally, be from the same laboratory to minimise any potential confounding due to variations in laboratory conditions, study conditions, animal suppliers, husbandry", and that historical data should be contemporary to the study being evaluated (eg within a period of up to around five years of the study).[46]

The BfR's glyphosate RAR represented a flagrant example of violating those rules when citing HCD to discount adverse findings. In practice, the BfR used a compilation of HCD stretching over a timespan of twenty-two years from seven different laboratories, comparing the results from a stressful housing condition (wire-bottom cages) of the historical controls with those of the glyphosate studies housed under less stressful conditions (eg solid-floor cages), while also neglecting the duration of studies (eighteen versus twenty-four months), which had an important influence on spontaneous tumour incidences.

Other official advisory bodies in EU Member States have contributed to the maintenance of the status quo. For example, when acting as rapporteurs, they have often invoked HCDs to discount positive toxicological findings in ways that violated the OECD and ECHA criteria, and dismissed evidence of increased tumour incidences when compared with concurrent controls. Specifically, such transgressions can be found in the carcinogenicity assessments in four out of nine other draft RARs reviewed by Clausing,[47] namely those for the active ingredients dimoxystrobin, folpet, phosmet and pirimicarb. Official institutions have frequently acted in ways that are inconsistent with the rules with which they claimed to comply.

Another important type of the failure in practically applying "the principles and methods of the science of regulatory risk assessment"[48] has been the willingness of European authorities to accept and rely on studies with high mortality rates during the course of those studies. The premature deaths of the animals entail, firstly, that many died too young to have provided sufficient data, and secondly, that the numbers of animals available for detailed end-of-study post-mortem examination are too small to provide sufficient data from which statistically significant effects might be derivable.

Carcinogenicity studies are long-term studies; they typically cover approximately 75% of the average life expectancy of laboratory rodents. The validity of the findings of such studies crucially depends on sufficient animals surviving to the end of the minimum study duration of eighteen or twenty-four months for mice and rats, respectively. Therefore, OECD guidance document No. 116 recommended:

[43] ibid.

[44] European Chemicals Agency (ECHA), "Guidance on the Application of the CLP Criteria" (2017, Version 5.0) <https://echa.europa.eu/documents/10162/2324906/clp_en.pdf>.

[45] Organisation for Economic Co-operation and Development (OECD), supra, note 37.

[46] European Chemicals Agency (ECHA), supra, note 44.

[47] P Clausing, "Chronically Underrated? A Review of the European Carcinogenic Hazard Assessment of 10 Pesticides" (Pesticide Action Network Germany and Health and Environment Alliance, 2019 Report) <https://www.env-health.org/wp-content/uploads/2019/10/October-2019-Chronically-Underrated-web.pdf>.

[48] Herzler et al, supra, note 2.

> For a negative result to be acceptable in a rat carcinogenicity bioassay, survival in the study should ideally be no less than 50% in all groups at 24 months ... In a mouse study, survival in all groups in the study should be no less than 50% at 18 months.[49]

Details from two RARs serve to illustrate violations of that requirement.[50] In the RAR of phosmet, the survival rate in a rat study was well below 50%, but it was nevertheless deemed acceptable and reliable by the authorities as indicating a lack of carcinogenicity. Survival rates at the end of the 108 weeks were 20%, 24%, 32% and 38% in males and 32%, 35%, 32% and 42% in females for the control, low-, mid- and high-dose groups, respectively.

Similarly, a rat study on pirimicarb with survival rates in males of between 35% and 48% was accepted. Ironically, for the mouse study, the following was noted: "In this study there is evidence of a carcinogenic potential of pirimicarb but with the limitations in the historical control data and reduced survival this data alone is not sufficient to conclude on carcinogenicity."[51]

In other words, in the rat study, where the Rapporteur Member State (the UK) should have taken low survival rates into account before accepting a putative negative finding, that criterion was ignored. However, in the mouse study, in a situation where survival rates were not significantly low, a positive finding was nonetheless dismissed by alleging reduced survival, even though reduced survival is not a legitimate criterion for exclusion in cases of positive findings of significantly increased tumour incidences.

Herzler et al criticised the CSS for arguing that there is "a necessity for further improving the protection of 'vulnerable groups'".[52] Their view was that "without a detailed assessment of which risks are currently deemed to be insufficiently addressed, it is hard to establish whether additional regulation might be necessary or existing regulation might need to be improved, and for which part of the population" (ibid). But that approximates to arguing that, until a quantitative risk assessment has been completed, it would be premature to regulate on the basis of partial incomplete information, which implies that precaution should never be exercised; but that is incompatible with EU legislation.

In relation to EDCs, Herzler et al implied that, before the CSS's approach could deserve to be adopted, and before any further particular measures are implemented, the Commission should comprehensively identify all toxicologically problematic chemicals; that approach is, however, directly antithetical to precaution. Herzler et al's perspective also irredeemably involves a value judgment – and not a scientific one – about how much of which kinds of evidence should be deemed necessary and sufficient before specific measures are adopted. Their value judgment, moreover, accords with industrial interests rather than prioritising the protection of public and environmental health.

IX. The BfR's misunderstandings and misrepresentations of the Chemical Strategy for Sustainability

Herzler et al complained that the CSS was biased, but they were seemingly unaware of their own biases, many of which are evident from the facts that they chose to emphasise and the indicators that they chose to highlight. For example, Herzler et al criticised the CSS for failing adequately to differentiate "risks" from "hazards". Historically, chemicals were typically restricted or banned only on the basis of a demonstrable risk given anticipated levels of exposure, not just on the basis of their intrinsic hazardous properties without reference to particular levels or frequencies of exposure. Herzler et al said correctly that

[49] Organisation for Economic Co-operation and Development (OECD), supra, note 37.
[50] Clausing, supra, note 47.
[51] ibid, p 21; BfR, *Renewal Assessment Report. Glyphosate*, Volume 3 B.6, p 107.
[52] Herzler et al, supra, note 2.

> it is trivial yet important to clearly distinguish between hazard, exposure and risk, as only the latter provides information on whether something is harmful (i.e. actually causes harm) or not. Amalgamating the terms "hazard" and "risk" leads to conceptual misunderstandings, with the consequence of fostering muddled conclusions and perceptions.[53]

However, the BfR team was itself blurring this distinction by failing to engage properly with the fact that some hazards – under the explicit provisions of EU legislation – have been officially categorised as unacceptable. For example, EU Regulation 1107/2009 states that a genotoxic, carcinogenic or reprotoxic pesticides "shall only be approved ... if it is not or has not to be classified ... as category 1A or 1B" (for mutagenicity, carcinogenicity or reproductive toxicity). This pivotal piece of legislation focuses on *hazard* categories, referring to their intrinsic toxicological properties.

The BfR itself risked disseminating "conceptual misunderstandings" by repeatedly stating that, in the case of glyphosate, IARC "only" provided a hazard assessment, while implying that the BfR had been more thorough by providing a risk assessment.[54] In practice, moreover, the BfR's judgment focused in particular on an important hazard characteristic when concluding that glyphosate is not carcinogenic. If the BfR had come to the same conclusion as IARC, under EU legislation no risk assessment would have been needed.

The Commission did not fail to distinguish risks from hazards; rather, it articulated an evaluative policy judgment that both sets of considerations can – and under certain conditions should – be adequate grounds for introducing or maintaining regulatory measures. The BfR team simplistically suggested that policy decisions can be made solely on scientific grounds and assumed that their chosen version of "the science" was incontestable. Claiming or even just assuming that only risks (which the BfR team interpret as quantified proven damage but not evidence of hazards) should be sufficient grounds for regulatory controls is unambiguously a normative policy judgment rather than an empirical finding.

X. Conclusion

To characterise the CSS's proposed changes to the prevailing regime as "unscientific" is to commit what academic philosophers helpfully call a "category error". The CSS is not intended to be and should not be misrepresented as a purely scientific judgment. It was a critical and historically informed policy judgment about the inadequacies and shortcomings of the prevailing regime and the incomplete, equivocal and contested corpus of scientific evidence on which it purports to be based. It advocated changes in risk assessment policies and provided a constructive strategic response to those shortcomings.

Alleging that the consequences of implementing the Commission's proposals would be "overprotective" entails making value judgments about how much protection is sufficient and about who should decide how much protection is enough. Questions of that sort inevitably invite the response: "enough for whom?". The BfR team had, in effect, claimed the right and authority to decide what should be deemed "sufficient". Herzler et al accused the CSS of being "inherently arbitrary", at the same time articulating their own arbitrary

[53] ibid.

[54] Bundesinstitut für Risikobewertung (BfR), "Mehr Sachlichkeit in der Diskussion um die EU-Wirkstoffprüfung von Glyphosat gefordert" (Mitteilung Nr. 25/2015 des BfR vom 28 Mai 2015) <https://www.bfr.bund.de/de/presseinformation/2015/25/mehr_sachlichkeit_in_der_diskussion_um_die_eu_wirkstoffpruefung_von_glyphosat_gefordert-195267.html>; Bundesinstitut für Risikobewertung (BfR), "Populäre Missverständnisse, Meinungen und Fragen im Zusammenhang mit der Risikobewertung des BfR zu Glyphosat" (Mitteilung Nr. 013/2016 des BfR vom 19 Mai 2016) <https://www.bfr.bund.de/cm/343/populaere-missverstaendnisse-meinungen-und-fragen-im-zusammenhang-mit-der-risikobewertung-des-bfr-zu-glyphosat.pdf>.

policy judgments while pretending that they were legitimated solely by reference to scientific considerations.

There are therefore good empirical grounds for concluding that current chemical regulatory regimes in the EU are not just suboptimal but seriously inadequate. The European Commission's CSS is a prudent response to the available evidence, although its full implementation will be challenging. Herzler et al's critique of the CSS and their attempted defence of the status quo were flawed in numerous conceptual and empirical respects. They misrepresented much of the scientific evidence and ignored lots more, and they misleadingly portrayed their position as if it were purely scientific when it was in fact replete with problematic normative assumptions and judgments.

Competing interests. The authors declare none.

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