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Center for Food Safety appreciates the opportunity to comment on EPA's Cumulative Risk Assessment Guidelines for Planning and Problem Formulation, on behalf of itself and its 970,000 members and supporters. Center for Food Safety (CFS) is a public interest, nonprofit membership organization with offices in Washington, D.C., San Francisco, California, and Portland, Oregon. CFS's mission is to empower people, support farmers, and protect the earth from the harmful impacts of industrial agriculture. Through groundbreaking legal, scientific, and grassroots action, CFS protects and promotes the public's right to safe food and the environment.

Introduction

It has long been recognized that the still predominant practice of assessing the risks of chemicals and stressors one at a time, in isolation, fails to capture the harms they cause in the real world, where multiple exposures (simultaneous and sequential) are the rule. Clearly, an assessment approach that cumulates exposure and risk across multiple xenobiotics is badly needed, and should become standard practice rather than the exception.[1]

While CFS welcomes EPA's draft Guidelines, we find it unfortunate that nearly half a century after the first Cumulative Risk Assessment (CRA) Publication Milestone in 1980 (Guidelines, Fig. 2, p. 3), EPA has gone no further in this document than to "describe considerations for evaluating when CRA is both suitable and feasible, and steps to plan a CRA when those conditions are met" (Guidelines, p. 1). As such, the limited scope of these Guidelines differs little from EPA's position a quarter century ago, when it published the first of a plethora of CRA guidance documents in 1997: Guidance on Cumulative Risk Assessment, Part 1, Planning and Scoping (Ibid., Figure 2, p. 3). Only the latter, older document portrays CRA as the wave of EPA's regulatory future,[2] while these Guidelines stress obstacles, limitations, uncertainties and resource constraints.

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[1] These comments focus on exposure to chemicals; CFS has signed on to comments led by EarthJustice that provide further discussion of how to address the interaction of chemical and non-chemical stressors, which causes harms in particular to environmental justice communities.

[2] Consider the opening passage: "The practice of risk assessment within the Environmental Protection Agency (EPA) is evolving away from a focus on the potential of a single pollutant in one environmental medium for causing

Most of the few examples of CRAs cited by EPA occurred decades ago, without the benefit of these Guidelines: assessing disinfectant/disinfection byproducts (year 2000), air pollutants and to some extent for Superfund sites (Guidelines, A-5 to A-6). In the realm of pesticides, four of the five full cumulative risk assessments that have been conducted thus far were completed from 1999 to 2007, 16 to 24 years ago. The fifth was published in 2011.[3] A screening level assessment of a sixth group (HPPD Inhibitors) was completed in 2021 (EPA HPPD Inhibitor CRA 6/30/21).

EPA needs to move beyond planning, scoping, frameworking, screening out, and re-start the process of cumulative risk assessments, which have tailed off dramatically in frequency over time, and progress towards making them the default rather than the exception.

Criteria for Grouping Chemicals for Cumulative Risk Assessment.

EPA has traditionally focused heavily on the structural properties of the chemicals and the biochemical nuances of the activity by which they cause harm as criteria for determining the group to assess cumulatively. The Agency has also appealed to the concept of toxicological similarity as the criterion for cumulative assessment. In contrast, scientists have long advocated an approach that groups chemicals by the adverse health outcomes they cause. The Guidelines do not resolve this tension, but rather appear to endorse a full range of criteria, which unfortunately gives rise to confusion regarding this foundational aspect of CRA, and provides support for continuing the narrowly circumscribed and unprotective CRAs of the past.

Structural Similarity

Structural similarity is a poor criterion for grouping chemicals for CRA, yet it is the starting point for many of those EPA has thus far conducted. Pesticide CRAs are designated by chemical family name, which usually identifies a common structural feature. Examples include organophosphates, N-methyl carbamates, chloroacetanilides and triazines. For instance, the family of triazine herbicides comprise elaborations on a six-member benzene-like ring structure with three nitrogen atoms replacing three of the carbons ($C_3H_3N_3$). Moreover, EPA's definition of the common mechanism group (CMG) from which pesticides are selected for cumulative risk assessments specifically cites "shared structural characteristics" as the first criterion in several cases, e.g. N-methyl carbamates, pyrethrins/pyrethroids and HPPD inhibitors.

The chief weakness of this criterion is that it has nothing to do, *per se*, with the adverse human health effects CRA's are conducted to assess and prevent. An NRC Committee informed EPA that a cumulative risk assessment of phthalates (esters of 1,2-benzenedicarboxylic acid) should be limited to those with ester chains of four to six carbon atoms, since other members of the group did not appear to negatively impact male reproductive development (the adverse health

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cancer toward integrated assessments involving suites of pollutants in several media that may cause a variety of adverse effects on humans, plants, animals, or even effects on ecological systems and their processes and functions." (p. 1).

[3] Accessible at: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides.

outcome of cumulative concern) (NRC 2008, p. 48). Similarly, EPA's CMG for "triazines" comprised only three members of the group (atrazine, simazine and propazine) and certain metabolites, while excluding seven triazines that were judged not to share the toxicity profile of the former three.

Applying structural criteria not only risks inclusion of inappropriate compounds in a CRA, more seriously it can lead to exclusion of dissimilar compounds that trigger a shared adverse health outcome, leading to a CRA that underestimates risk (EFSA 2013). The NRC committee noted above found that "a focus on phthalates to the exclusion of other antiandrogens (or other more esoterically acting agents) not only would be artificial but could imply serious underestimation of cumulative risks posed by agents to which there is coexposure" (NRC 2008, p. 110). Another example is EPA's separate CRAs for two structurally-defined groups of pesticides – organophosphates and N-methyl carbamates – that share inhibition of acetylcholinesterase (AChE) as at least one of their toxic modes of action. The risks posed by exposure to members of both of these pesticide families is likely underestimated by assessing them separately. In contrast, the European Food Safety Authority grouped both families together in its cumulative risk assessment of pesticides that inhibit brain and/or erythrocyte acetylcholinesterase (EFSA 2019, 2021).[4] Therefore, we urge EPA to move away from using common structural characteristics as a criterion for grouping chemicals for a CRA.

Common Mechanism or Mode of Toxicity
The unspoken assumption behind use of common structural features as a criterion is that they sometimes map onto a common mechanism or mode of toxicity. For instance, a toxic mechanism that involves blocking a receptor or inhibiting an enzyme often requires that the toxic molecule have a particular three-dimensional configuration that fits the receptor or enzyme active site, and the chemicals that fit often include members of a particular family with structural similarity.

While mode of toxicity is a somewhat more useful criterion than chemical structure, it is still too heavily focused on the molecule, and the biochemical nuances of how it damages a tissue or organ, distracting attention from the adverse health outcome(s) for which the CRA is being conducted. The NRC found it "unnecessary" to take account of mode of action in the process of grouping chemicals for cumulative risk assessment, in part because of the difficulty of defining reliable criteria for similarity of mechanisms of action (NRC 2008, p. 108), but more fundamentally because it results in underestimation of risk.

> "…a focus on phthalates to the exclusion of other antiandrogens (or other more esoterically acting agents) not only would be artificial but could imply serious underestimation of cumulative risks posed by agents to which there is coexposure."
> (NRC 2008, p. 110).

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[4] Moreover, EFSA included non-insecticidal organophosphorous pesticides – ethephon (plant growth regulator) and tolclofos-methyl (fungicide) – based on their inhibition of acetylcholinesterase. EPA excluded both from its OP CRA, perhaps because the Agency limited its scope to OP insecticides.

This is because the adverse outcomes of phthalates – the constellation of developmental defects ensuing from insufficient androgen during fetal development – also result from exposure to different chemicals acting via different molecular mechanisms of actions. Thus, for the purposes of CRA, NRC groups together chemicals that cause androgen insufficiency syndrome via three distinct mechanisms: androgen-receptor antagonists, mixed-function inhibitors (which both reduce fetal testicular testosterone production like phthalates, but also act as androgen receptor antagonists), and inhibitors of 5-alpha reductase, the enzyme that converts testosterone to dihydrotestosterone (NRC 2008, pp. 53-54). Later, the recommended CRA group is expanded to include azole fungicides (ketoconazole, tebuconazole and propiconazole), polybrominated diphenyl ethers, TCDD and some PCBs, for all of which there is strong evidence of eliciting some or all of the symptoms of androgen insufficiency syndrome (Ibid., Table 5-2, p. 124-125).

Mechanisms of action known from experiments on adult animals may be particularly misleading in the developmental context (Slotkin 2006). For instance, scientists distinguish between the effects of organophosphate insecticides (OPs) on the nervous systems of adult and developing rats, finding "a complete dichotomy between the systemic toxicity of organophosphates and their propensity to elicit developmental neurotoxicity" (Slotkin et al. 2006). The acute effects of OPs to mature animals is due to their common inhibition of acetylcholinesterase (AChE), while exposure during development has varying effects via different mechanisms, dependent on developmental stage. For example, in the developmental context, chlorpyrifos directly affects both muscarinic and nicotinic cholinergic receptors, alters the expression and function of serotonin receptors, and interacts with signaling intermediates such as G proteins and adenylyl cyclase (Slotkin 2006). Despite the commonality of AChE inhibition in their systemic activity, OPs exhibit differential developmental neurotoxic effects (Slotkin et al. 2006, Slotkin et al. 2008). These examples highlight the pitfalls of conducting CRAs based on a (presumed) common mechanism of toxicity.

On a practical level, too, the mechanism and even mode of toxicity of a chemical is often poorly understood, making it difficult to group chemicals for CRA's on this basis. The European Food Safety Authority note that "a fully elucidated mechanism of toxicity is only available for a few chemicals, one example being cyanide," and that while more chemicals have a known mode of action, such MoA information will not be routinely available because registrants are not required to submit such data in order to obtain regulatory approval of chemicals (EFSA 2013, p. 21).

CFS agrees with the European Food Safety Authority (EFSA), which a decade ago turned away from the common mechanism of toxicity approach, and instead endorsed common adverse outcomes as the chief criterion for grouping chemicals for CRAs:

> **"The Panel comes to the overall conclusion that distinctions between similar and dissimilar MoA are fraught with great conceptual and practical difficulties and are of limited relevance in cumulative risk assessment practice. Pesticides that produce common adverse outcomes on the same target organ/system should be grouped together in CAGs, and their combined effects assessed by using the concept of dose addition as a pragmatic and conservative default approach for the purpose of**

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assessing cumulative risk in relation to MRL setting or risk assessment of chemical mixtures in practice, as already proposed in the 2013 EFSA Opinion on CAGs (EFSA PPR Panel 2013, p. 31, emphasis in original)

Common adverse health outcomes
For many years, scientists have been urging that xenobiotics be grouped for CRA's based on common adverse health outcome rather than structural similarity or common mechanism/mode of action, and assessed via dose addition rather than independent action (e.g. Kortenkamp et al. 2007, NRC 2008).

The NRC describes this as starting from "the physiological process, not mechanisms or modes of action of the chemicals to be assessed" (NRC 2008, p. 124). Starting from physiology, "a number of relevant end effects suggest themselves, and these should provide the basis for grouping." In the case of phthalates and other antiandrogens, the adverse outcome is identified as a syndrome comprising closely related effects on male reproductive tract development, including cryptochordism, hypospadias, reduced fertility and reduced anogenital distances: "All chemicals that can induce some or all of the effects that make up the androgen-insufficiency syndrome should be subjected to CRA." (Ibid.)

It is by now well-established that the adverse effects of chemicals affecting a common target organ or tissue in similar ways are often cumulative, and best predicted by dose addition, even when the compounds have dissimilar modes of action (EFSA 2013, Rider et al. 2010). As a result, exposure to a group of such chemicals, even at concentrations that are below the no observed adverse effect level (NOAEL) for each member of the group, often cumulate to exert adverse effects, as demonstrated most strikingly by EPA scientists for male reproductive tract impairments (Conley et al. 2018, Conley et al. 2021).

Toxicological similarity
EPA appeals to the concept of "toxicological similarity" as the criterion for grouping chemicals for CRAs, and maintains that "chemicals are toxicologically similar if the chemicals have a common mode of action, *or* if they affect a common target organ" (Guidelines, p. 24, emphasis added). However, in practice EPA only takes the first criterion – common mode of action (among a group of structurally similar compounds) – seriously, despite the established scientific consensus to conduct CRAs on compounds with common adverse outcomes.

This is seen most clearly with pesticides, for which most of EPA's CRAs have been conducted. EPA undertakes a three-step process. In the first step, a particular family of structurally similar chemicals associated with some particular adverse effect or syndrome is chosen. Then, EPA chooses a subset of those chemicals that produce that effect (based on available data), and do so in precisely the same way. This is called the "common mechanism group" (CMG). In the final step, EPA forms the "cumulative assessment group" (CAG), which comprises those CMG members whose uses, routes, and pathways of exposure will present sufficient potential for exposure and hazard to justify inclusion in the cumulative risk assessment.

The Agency has not changed its approach to keep pace with expanding knowledge. This is seen in the criterion for CRA grouping (boldface font below), which has not changed by a single word from the batch of CRAs completed in the mid-2000's to the latest screening-level CRA in 2021:

> "A cumulative risk assessment begins with the identification of a group of chemicals, called a common mechanism group, that induces a common toxic effect by a common mechanism of toxicity. **Pesticides are determined to have a "common mechanism of toxicity" if they act the same way in the body – that is, the same toxic effect occurs in the same organ or tissue by essentially the same sequence of major biochemical events"[5]**

> "The first step is the identification of a CMG, which induce a common toxic effect by a common mechanism of toxicity. **Pesticides are determined to have a "common mechanism of toxicity" if they act the same way in the body – that is, the same toxic effect occurs in the same organ or tissue by essentially the same sequence of major biochemical events." (**HPPD inhibitors CRA, 6/30/21, p. 4)

EPA has it backwards. Rather than define a particular adverse health outcome or syndrome of public health significance, then identify chemicals that elicit it to form a cumulative assessment group for CRA, EPA chooses for CRAs only those members of a single, structurally-defined chemical family that act in precisely the same biochemical manner to produce the same effect.

This is precisely the approach criticized by the NRC 15 years ago – the NRC that EPA charged with advising it on how to conduct a CRA on phthalates, and perform CRAs more generally, and which is cited frequently in these Guidelines:

> "The committee concludes that the criteria applied by EPA are too narrow and restrictive because they leave out other chemicals that can disrupt male sexual differentiation but in ways that differ in some respects from phthalates (see Chapter 3) …. Judged from such a perspective, a focus on phthalates to the exclusion of other antiandrogens (or other more esoterically acting agents) not only would be artificial but could imply *serious underestimation of cumulative risks posed by agents to which there is coexposure*." (NRC 2008, p. 110)

The European Food Safety Authority is also critical of the U.S. "tradition" of conducting cumulative assessments based on structural similarity:

> "Especially in the USA there has been a tradition of employing criteria derived from features of chemical structural similarity for the assessment of combinations of pesticides (USEPA, 2002). Only active substances that are structurally similar are assessed together, with the implicit assumption that they must meet the criteria of similar action, and therefore warrant the use of dose addition. Without further evidence, chemicals that fall outside the chemical space of interest are regarded as acting together according to the principles of independent action. With the additional

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[5] Accessible at: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides.

assumption that exposures are below threshold doses, assessments of cumulative risks are then considered unnecessary." (EFSA 2013, p. 12).

EPA will argue that, in the realm of pesticides, it is forced to drastically limit the scope of chemicals assessed cumulatively by the "common mechanism of toxicity" phraseology of the Food Quality Protection Act (FQPA) (Guidelines, p. viii, ft. 2). This is not true. Nothing in the FQPA constrains EPA to adhere dogmatically (and *verbatim*) to a definition of "common mechanism of toxicity" that it first developed two decades ago. On the contrary, regulatory interpretations of statutory language must evolve with advances in scientific understanding.

Here, EPA can and must construe "mechanism" more broadly. For instance, when two chemicals affect different sites of an effector chain, leading to a common adverse outcome, the chemicals share a common mechanism of toxicity by virtue of the common biological pathway or network they act upon, and the common downstream adverse effect(s) they cause. Another example of how this term should be expanded is found in EPA's proposed cumulative assessment of six phthalates, which is based on their common disruption of fetal testicular steroidogenesis when exposure occurs during a critical window of development (EPA 2023a, pp. 91-92). The disruption of fetal testicular steroidogenesis is the common mechanism by which the six phthalates exert their toxic developmental effects – effects which include reduced production of testosterone by the fetal testis, reduced anogenital distance and hypospadias. This is true whatever nuanced differences there may be in the precise molecular underpinnings of their respective activities.

Pesticides and other chemicals can and must also be assessed cumulatively when their common mechanism of toxicity is elicitation of a shared syndrome. This is the case for the developmental effects of phthalates mentioned above, which are consistent enough to be described as the "phthalate syndrome." A syndrome-based CRA is not only permissible under the Toxic Substances Control Act (TSCA). There is already precedent for this approach under FIFRA, in EPA's 2011 CRA for pyrethrins/pyrethroids, where the ultimate basis for the CRA is the T-syndrome or CS-syndrome elicited by Type I and Type II pyrethroids, respectively (where T stands for tremor and CS for choreoathetosis and salivation) (EPA 2023b, p. 10).[6]

EPA provides a helpful gloss on the broad range of possible meanings it attaches to the term "toxicological similarity" in a recent document outlining principles for the conduct of CRAs under the TSCA (EPA 2023b, pp. 9-10). The term can refer to chemicals that exhibit (from most to least restrictive definition) identical toxicodynamics, or similar toxicodynamics; those that elicit a shared syndrome, or a shared apical outcome (absent knowledge of molecular events); those that affect the same target organ; or have structural similarity or have similarly shaped dose-response curves in comparable toxicity studies. EPA presents these different understandings as varying levels of evidence that the chemicals in question are toxicologically similar and thus merit a cumulative assessment.

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[6] See also EPA Pyrethrin/Pyrethroid CRA 2011, p. 11, https://www.regulations.gov/document/EPA-HQ-OPP-2011-0746-0003.

EPA should revise the Guidelines to make it clear that in no case should CRAs be limited to chemicals that meet the more restrictive definitions of toxicological similarity. As discussed above, xenobiotics need not exhibit identical or similar toxicodynamics in order to contribute to a shared syndrome, apical outcome or target organ effect. Retaining these definitions diverts attention from the adverse health outcome, the prevention of which should be the focus of the CRA, and provides illicit justification for dramatically narrowing the group of chemicals subject to cumulative risk assessment, which can thereby lead to "serious underestimation of cumulative risks posed by agents to which there is coexposure" (NRC 2008, p. 110).

Dose Addition as Default for CRAs of Chemicals with Dissimilar Modes of Action

In the Guidelines, EPA perpetuates a fundamental misunderstanding that suggests dose addition only be used in CRAs when the cumulative assessment group members have a shared mode or mechanism of action; whereas response addition is used when the chemicals being assessed cumulatively have dissimilar modes of action (Guidelines, p. 24). It is interesting to note that EPA's references for this statement are outmoded guidance documents from the years 1986 and 2000. EPA must correct this outdated approach in light of voluminous evidence that the impacts of chemicals which exert common adverse effects but have dissimilar modes of action are most often best predicted by dose addition rather than independent action/response addition. As noted above, this was demonstrated conclusively for antiandrogens 13 years ago, and by EPA scientists no less, who demonstrated dose-additive effects of antiandrogens (phthalates, various pesticides) with multiple different modes of action (Rider et a. 2010). In another study, EPA scientists demonstrated that mixtures of antiandrogens acting via 5 different molecular initiating events nevertheless produced additive effects on male reproductive tract development at doses of each far below that known to cause such effects individually (Conley et al. 2018). These are just a few of the multitude of studies demonstrating similar results (EFSA 2013). It is critical that EPA dismiss the presumption of independent action when dealing with chemicals that have dissimilar modes of action because it has been proven repeatedly that mixtures of dissimilarly acting chemicals, at doses below their respective no observed adverse effect levels (NOAELs), nevertheless cause harms that are not predicted by independent action, but are often better estimated by dose addition (Kortenkamp et al. 2007, Christiansen et al. 2019, Conley et al. 2021).

CRAs Based on Common Adverse Outcomes

The scientific community and the European Food Safety Authority have advanced far beyond EPA in reorienting the cumulative risk assessment process away from structural similarity/common mode of action to the shared adverse health outcomes the prevention or mitigation of which is the ostensible goal of CRAs. Such efforts are still primarily limited to the realm of pesticides, but some scientists are breaching regulatory silos and investigating the common adverse effects of pesticides, industrial chemicals and other substances.

Over a decade ago, EFSA commissioned several reviews of registrant-submitted toxicological data on pesticides with the aim of identifying cumulative assessment groups of active ingredients with shared effects on organs or tissues at different levels of biological organization, for the purpose of outcome-based CRAs. For instance, Nielsen et al. (2012) produced a remarkably comprehensive, 300-page document that identifies compounds that affect different

organs or tissues (CAG level 1); have specific classes of effects on that organ/tissue (CAG level 2); and exhibit common mode (CAG level 3) or mechanism (CAG level 4) of toxicity with respect to effects on that organ/tissue.

On the basis of this and similar reviews, EFSA has already formed outcome-based cumulative assessment groups and completed several outcome-based cumulative risk assessments. Other scientists, including those with EPA, have conducted studies along similar lines. Perhaps the strongest evidence of need for an outcome-based CRA is male reproductive impairment triggered by developmental exposure, which is discussed above in relation to phthalates. Other organs and systems that merit priority for outcome-oriented CRAs are briefly surveyed below.

Thyroid gland and hypothyroidism
EPA scientists have demonstrated cumulative effects of a mix of chemicals that disrupt thyroid hormone homeostasis. Crofton et al. (2005) exposed rats to a mixture of 18 thyroid hormone-disrupting chemicals – dioxins, dibenzofurans and PCBs – and demonstrated additive or synergistic depression of serum thyroxine concentrations (depending on dose), despite the chemicals acting via different mechanisms of action. The European Food Safety Authority defined a cumulative assessment group (CAG) of 128 pesticides, metabolites or degradation products for hypothyroidism, defined as an altered function of the thyroid gland resulting in follicular cell hypertrophy, hyperplasia and neoplasia (EFSA Thyroid CAG 2019); a cumulative dietary risk characterization was then conducted with this CAG group, utilizing residue data and estimates of exposure for 10 distinct populations (EFSA Thyroid CRA 2020).

Liver and non-alcoholic fatty liver disease
The liver is the body's primary detoxification organ, and many industrial chemicals and pesticides are hepatotoxic. The most common hepatic pathology induced by chemicals is fatty liver (Al-Eryani et al. 2015) – the accumulation of lipids in liver cells – which can progress to more serious conditions, steatohepatitis and cirrhosis, which in turn are the most important risk factors for liver cancer (Wahlang et al. 2013). According to EPA scientists, fatty liver disease is "a growing epidemic" that affects 20-30% of the U.S. population (Angrish et al. 2009), while the incidence of liver cancer it predisposes to tripled from 1975 to 2005 (Altekruse et al. 2009).

Fully one-third of workplace chemicals in the U.S. (228 of 677) are hepatotoxic (Tolman and Sirrine 1998). Nearly 10% of the pesticides in EPA's pesticide toxicity database (42 of 437) induce fatty liver. And eighty-one other chemicals have similar effects. Thus, "fatty liver may be the most common pathologic hepatic response to chemical exposure" (Al-Eryani et al. 2015[7]). Triazole fungicides deserve particular consideration for their multiple adverse impacts on the liver, including lipid accumulation (CFS 10/4/21).

Given the liver's role in detoxification, the large number of xenobiotics that elicit fatty liver, the epidemic emergence of fatty liver disease, and the gravity of its sequelae, liver steatosis should

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[7] Results based on searches of EPA's Toxicological Reference Database (ToxRefDB), which stores pesticide registration toxicity data from animal studies over the past 30 years; and the National Toxicology Program's Chemical Effects in Biological Systems (CEBS), which warehouses toxicological data from approximately 9,000 rodent studies from academic, industrial and governmental laboratories.

be a prime candidate for an outcome-based CRA. EFSA took a step in this direction by forming a cumulative assessment group of 144 pesticides for hepatic steatosis, and assessing acute and chronic risk of steatosis based on hazard (using relative potency factors) and dietary exposure data for specific European populations (Crepet et al. 2019). The caveats to this study is that it seems to be based entirely on registrant-submitted animal study data, without incorporation of data from independent studies; it encompasses only pesticides and not the many industrial chemicals that induce fatty liver; and only dietary exposure is considered, whereas of course residential and occupational exposures (dermal, inhalational) will often be much higher. Finally, human epidemiology should be considered, wherever available. Even so, the outcome orientation of the CRA is a step in the right direction.

Kidney and renal tubule damage

Kidneys filter and process blood, removing waste products and toxins for elimination in urine. As part of the kidney apparatus, renal tubules come into intimate contact with toxins on their way out of the body, and thus it is not surprising that "the large majority" of kidney toxins target renal tubules (Commandeur and Vermeulen 1990), and tubulointerstitial injury is the best indicator of impaired renal function (Nath 1992). Chronic kidney disease is increasing in prevalence globally, and afflicts more than one in 7 Americans (Kataria et al. 2015, CDC 2019a). The incidence of the most common form of kidney cancer – renal cell carcinoma, which originates in renal tubules – has increased five-fold since 1971 in the U.S. (Cairns 2011).[8]

Like the liver, the kidney and in particular renal tubule degeneration should be a focus of an outcome-based CRA. 119 pesticides are documented as having adverse effects on the kidney (CAG Level 1), with 50 of those causing tubular cell degeneration/cell death (CAG Level 2a) (Nielsen et al. 2012, pp. 93-95).

Breaking Through Regulatory Silos

Fifteen years after the NRC report on phthalates (NRC 2008), EPA has finally begun the task of conducting a cumulative risk assessment. While this is welcome news, it is also long overdue. And EPA did not follow the NRC's recommendation to expand conduct a physiologically-based CRA that included not only phthalates, but also azole fungicides (ketoconazole, tebuconazole and propiconazole), polybrominated diphenyl ethers, TCDD and some PCBs, all of which elicit some or all of the symptoms of androgen insufficiency syndrome (Ibid., Table 5-2, p. 124-125).

CFS recognizes that breaking through regulatory silos is difficult, but in the age of ubiquitous environmental contamination with a multitude of PFAS and other industrial chemicals, widespread presence of residues of roughly 400 pesticides on foods, not to mention their frequent presence in surface and groundwater, it is becoming increasing necessary to consider the cumulative effects of this widespread and growing exposure to chemicals that do not respect regulatory boundaries.

The Food Quality Protection Act provides for cumulative assessments of pesticides and "other substances" that share a common mechanism of toxicity, which would permit EPA to alter the

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[8] Increased detection is not sufficient to explain this five-fold hike; mortality from renal cell carcinoma has doubled over the same time period.

conditions of exposure to a pesticide or group of pesticides if the cumulative exposure to it/them and other xenobiotics that have similar adverse outcomes exceed a safe exposure level.

We urge EPA to move ahead to orient cumulative risk assessments to adverse health outcomes, as discussed in these comments, and broaden them to match the exposures Americans experience.

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