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The risk of chemical cocktail effects and how to deal with the issue

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Over the past one hundred years, the number and volume of industrial chemicals introduced into the environment has increased exponentially. This has had an irreversible anthropogenic impact on Earth, potentially threatening planetary stability as well as human health. In a provocative feature article in *Nature* back in 2009, a group of scientists argued that, in order to maintain planetary stability, we must operate within set planetary boundaries—a total of nine, all of which are influenced by human activity.[1] Chemical pollution was one specified threat, but could not be quantified due to the complexity of the issue, the large number of chemicals and organisms involved, and the intricacies of all the possible interactions and outcomes. A recent review on the topic concludes that chemical pollution is already so significant that ecosystems and human health are under major stress, to the point of 'transgressing the safe operating space'.[2] Thus, a lessening of the chemical burden currently affecting the environment and humans is called for.

Here the focus is more on humans, rather than planetary boundaries. That is, how does direct exposure to chemicals affect human health? Man-made chemicals are now integral to modern societies and tens of thousands of chemicals are continuously manufactured and used across the world. In the USA, an estimated 83 000 chemicals are currently inventoried,[3] whereas in the European Union the number is estimated to be somewhat smaller, at 40 000–60 000. Thus, humans are potentially exposed to a significant number of chemicals from different sources, which significantly contribute to the human exposome; the total environmental exposure from conception onwards. Sources of exposure include foods and beverages, food packaging materials, furniture, clothes, cleaning products, sunscreens, cosmetics, electronic equipment, paints, building materials; and the list goes on. Chemicals can thus enter our bodies by us ingesting contaminated foods and drinks, breathing polluted air containing dust particles, or by absorbing constituents of creams and cosmetics applied to the skin. Additionally, persistent environmental chemicals can accumulate in tissues over time. This is of particular concern for animals at the upper end of the food chain, including humans, since the concentration of compounds can increase progressively up through the food chain by the process of bioamplification.[4] Thus total exposure can magnify by exposure to many low-concentration compounds over time, but this is really difficult to assess, not least when evaluating multiple exposures and outcomes in human subjects by epidemiological approaches.[5]

Biomonitoring studies have shown that the average human carries a footprint of several hundred chemicals, including dioxins, metals, phthalates, parabens, pesticides, poly-brominated and poly-fluorinated compounds, and polycyclic aromatic hydrocarbons. We may only have seen the tip of the iceberg, however, as this list only includes well-known chemicals cherry-picked for resource-demanding monitoring programmes. For instance, 2–3000 fluorinated chemicals exist, but only a few are included in the screening programmes. This is also exemplified by a study investigating the chemical burden in 10 newborn babies in the USA: each child had more than 200 chemicals in the umbilical cord blood.[6] This is in itself a high number, but considering that merely 400 chemicals were screened for, scores of chemicals could have been missed. The only comforting part of these studies is that most chemicals are present in our bodies at very low levels. But do 'low levels' necessarily equate with 'safe levels'?

A growing body of evidence suggests that many chemicals at low doses can add up to cause adverse effects, effects otherwise not seen if chemicals were present alone or in small numbers. This is typically referred to as the cocktail, or mixture, effect. Unfortunately, and despite the fact that cocktail effects have been observed in various experimental models for decades,[7] chemical risk is traditionally assessed on a one-by-one basis. This approach overlooks the potential for chemicals to 'join forces' to cause an effect, even at very low doses, and completely disregards the exposome concept. Therefore, conventional risk assessment practices most likely underestimate the human hazard of low-dose chemical exposure.

Animal studies have established that cocktail effects occur for many environmental chemicals including phthalates, parabens and pesticides. For example, rats exposed in utero to mixtures of antiandrogenic compounds show clear dose-additive effects on male reproductive end points, such as reduced anogenital distance and increased nipple retention, both of which are signs of feminisation.[8 9] Disrupted reproductive development was observed in male sheep offspring following fetal exposure to pollutants from pregnant ewes feeding on pastures treated with human sewage sludge.[10] Also, cocktail effects were recently shown in rodents exposed postnatally to low-dose mixtures, affecting parameters such as hormone synthesis and metabolic homoeostasis.[11] These studies provide good evidence for low-dose cocktail effects and show that they should be of general concern. But what is the evidence for low-dose cocktail effects in humans?

Cause–effect relationships can be difficult to prove in humans and this is complicated further by the time-lag between exposure during fetal life and adverse effects that may occur in adulthood. Clear evidence exists for adverse effects of single chemicals in humans, often as a consequence of environmental tragedies. Evidence for low-dose cocktail effects, however, is far more difficult to establish. Nevertheless, a growing number of studies are telling a story in which low-dose exposure does cause adverse health effects. For instance, many chemicals are associated with neurodevelopmental disabilities, and there is a strong correlation between low-dose pesticide exposure in babies and later IQ scores.[12] Maternal urinary phthalate levels correlate with shortened anogenital distance in newborn boys—a proxy measurement of fetal feminisation and late-life reproductive health issues.[13] Furthermore, there is a strong association between low-dose chemical exposure measured in breast tissue and breast cancer.[14] Although some of these low-dose effects can seem modest at first glance, they may significantly influence a person's quality of life.

Recently, we completed a large project on chemical cocktail effects, spearheaded by the National Food Institute, Technical

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University of Denmark. We found further evidence that low-dose cocktail effects are of real concern to humans and that chemicals affecting similar adverse outcomes often act additively when present together in mixtures. We also found that these additive effects can be predicted with reasonable accuracy using mathematical models, given that prior knowledge on single-chemical exposure levels and hazardous effects exist. And here lies one of the great challenges in addressing cocktail effects in chemical risk assessment: among the 40–80 000 chemicals currently in use, we only have adequate information to perform a full risk assessment for a maximum of 1000. This sizeable data gap is a real bottleneck for predicting cocktail effects. Therefore, more data must be gathered from a substantial number of uncharacterised chemicals. This task is likely unfeasible using only traditional animal-based methods, at least within a relatively short time-frame. Hence, improved and faster chemical risk assessment strategies are needed to test emerging and existing individual chemicals for which we lack knowledge. So how do we deal with this significant challenge?

No doubt, we need a paradigm shift in how to risk-assess chemicals in the future. To this end, we wish to highlight four key points:

- The legislation on chemical risk assessment needs to be updated to consider cocktail effects, ideally as a joint European or global venture.
- A gradual transition from animal-based testing strategies towards largely animal-free, high-throughput and high-content imaging strategies is needed. This would not only alleviate the considerable burden of current and resource-heavy strategies, but also significantly speed up the process.
- Computational approaches should be central to the shift away from the current paradigm. For instance, in silico strategies such as physiologically based kinetic models and predictive models based on chemical structures will continue to play more important roles.
- There is a strong need to gather more exposure data from humans using ever more cost-effective and sensitive equipment.

In essence, to predict the potential adverse health effects of chemical cocktails, we must first have a certain amount of prior knowledge on single chemicals. When faced with roughly 80 000 chemicals and the intricate workings of the human body, or wildlife for that matter, this can seem an impossible task. Nevertheless, developing novel risk assessment procedures to ensure a sustainable future for humans and the planet seems a worthy task, albeit an extremely challenging one. But rather than surrendering to the challenge, we should focus our attention on overcoming it sooner rather than later. As the late cartoonist Walt Kelly said: 'We are now confronted with insurmountable opportunities'.

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