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How are endocrine disrupting properties of non-active substances currently assessed – and what are the challenges?

Yuzhu (Celia) Wei and Ingrid Sterenborg, experts in registration services and risk assessment at Triskelion, discuss the present practice of assessing endocrine disrupting properties of co-formulants and suggest possible improvements

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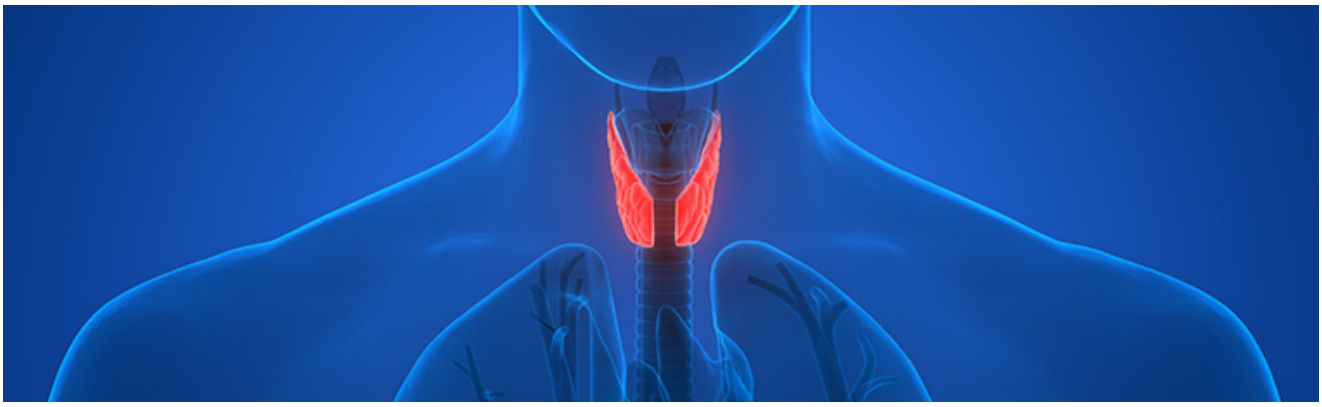

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In 1999, in response to the growing awareness of the adverse impact of endocrine disruptors on humans and wildlife, the European Commission published its Strategy for endocrine disruptors.

Three years later, the WHO released its definition of endocrine disrupting chemicals. EDCs, this said, are 'exogenous substances or mixtures that alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub) populations'.

These developments were followed by intensive scientific work on the presence and impact of EDCs.

One of the consequences of this work has been that the EU has made its legislative framework regulating EDCs more stringent. The plant protection and biocidal products Regulations have, for example, been expanded to list scientific criteria to help identify endocrine disruptors. Further regulations – (EU) 2017/2100 and (EU) 2018/605 – clarified these criteria. In addition, EDCs can now be identified under REACH as substances of very high concern using the Regulation's 'equivalent concern' rules. Specific studies on identifying endocrine disrupting properties are currently being considered as future requirements under REACH.

Assessing EDCs

Although legislative acts have been available for years, they have been hampered by the fact that assessing an EDC remains challenging for several reasons, including:

- EDCs commonly have low-dose effects, delayed effects, and non-monotonic responses, which the standardised regulatory toxicological endpoints may not capture;
- the Efsa/Echa guidance from June 2018 focused on four modalities: oestrogen (E), androgen (A), thyroid (T) and steroidogenesis (S). In reality, EDCs can cause adverse impacts via many more modalities. Furthermore, the number of studies following these guidelines are still deficient; and
- interpreting available literature, as required, is extremely difficult due to insufficient clarity about the scientific relevance of findings and criteria.

Assessing non-active substances under the BPR and PPPR
Most of the regulators' and scientists' attention has been on active substances in biocidal or plant protection products. But how can non-active substances used in these products be evaluated?

The plant protection products Regulation

As well as active substances, plant protection products include the following non-active substances:

- safeners;
- synergists; and
- co-formulants.

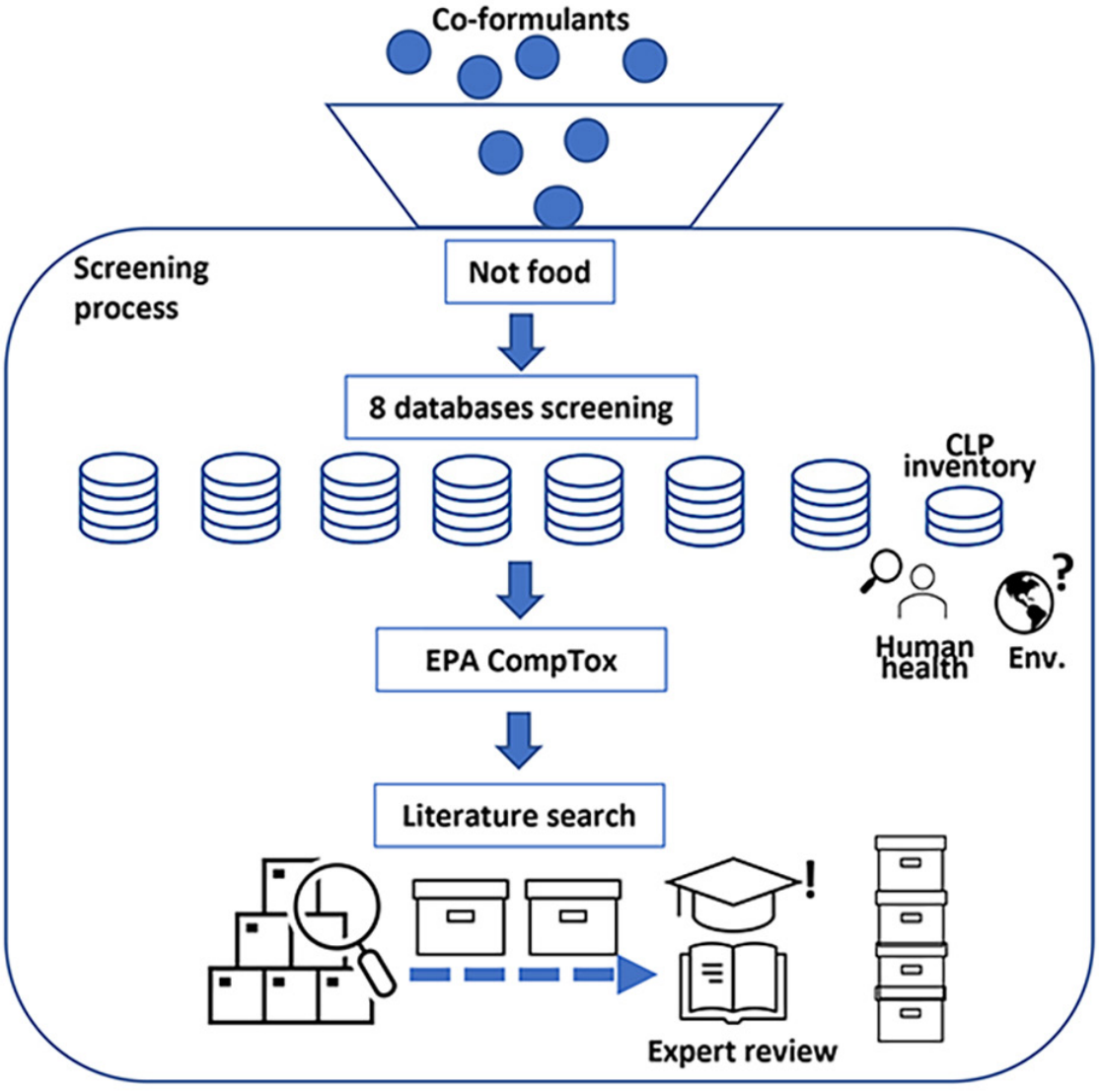
Safeners and synergists are evaluated according to the same EDC criteria used for active substances (in line with the Efsa/Echa guidance). The endocrine disruption of co-formulants falls under the criteria of very high concern as mentioned in Commission Regulation (EU) 2021/383. Co-formulants that have endocrine disrupting properties are considered unacceptable and are listed in Annex III of the PPPR.

The biocidal products Regulation

According to the BPR, a biocidal product should be considered endocrine disrupting based on the properties of both its active substances and its co-formulants – which make up all the non-active substances used in biocides. A co-formulant's EDC properties are assessed at the product authorisation stage. Therefore, according to the guidance, no detailed assessment of a co-formulant is required, unless there are suspicions, based on existing knowledge and available scientific information, that it has endocrine disrupting properties.

A stepwise approach was developed by the UK competent authority in 2019 to check the potential EDC properties of co-formulants. This approach has been widely adopted and forms the basis of Echa's competent authorities' guidance

Figure 1: Process and challenges of screening the EDC properties of co-formulants in biocidal products



contained in document CA-March21-Doc.4.3: Proposal to bridge the endocrine disruptor assessment of biocidal non-active substances with REACH screening and assessment.

Experience and challenges of the current stepwise approach

If the co-formulant is a food/foodstuff material as defined into the EU's food Regulation (EC) No 178/2002, it does not have to be studied further (no indications of EDC properties). If the co-formulant is not a food/foodstuff material, the substance will be screened in eight databases that indicate possible endocrine disrupting properties:

- the list of exclusion criteria under the BPR;
- the list of active substance, safeners and synergists under the PPPR;
- the list of substances of very high concern (SVHCs) under REACH;
- US EPA Endocrine Disruptor Screening Program in the 21 Century (EDSP21);
- the community rolling action plan (Corap);
- the public activities coordination tool (PACT);
- the Endocrine Active Substances Information System (EASIS); and
- the classification, labelling and packaging (CLP) inventory.

As EASIS 2.0 is under development, and EASIS 1.0 has been discontinued, this database is not used at the moment.

The CLP inventory

Screening the seven remaining databases for EDCs is a significant amount of work, especially in the case of biocidal products that contain many co-formulants.

But it is the CLP inventory that can be the most challenging. Unlike the other databases, it does not give a clear "Yes" or "No" to indicate a substance's endocrine disrupting properties.

The inventory has its relevant classifications – carcinogenic 1A, 1B and 2, Stot RE 1, Stot RE 2, reprotoxic 1A, 1B and 2 – are selected before downloading.

This selection reduces the amount of the data produced but still leaves a large file that sometimes may not be downloadable. In such a case, an EDC properties assessor will have to go through Echa's service desk to get the file.

As well as the technical challenges the CLP inventory presents, there is also a scientific problem. Most of the CLP classifications' H codes do not indicate a substance's actual effects. For example, the H370 code indicates a substance causes damage to organs. Such a substance may be toxic to the central nervous system, which is potentially EDC relevant. However, the same code may apply to a substance that has a toxic impact on the lungs, and which is therefore unlikely to be EDC relevant.
To further complicate this, the same substance can show different classifications (and H codes) where no harmonised classification is available. The scientific validity of these classifications can be uncertain.

To reduce a company's workload, limiting the screening to the top three databases, or ignoring entries covering less than, for example, 10% of all classifications, may be a practical option but one that is short of scientific support.

Overall, the large amount of unclear information in the CLP inventory significantly increases the workload of an EDC assessment because substances with many co-formulants can show a "match" result here but not in the other six databases. The guidance suggests checking "matched" substances in the US EPA's CompTox Chemical Dashboard and literature to rule out potentially endocrine disrupting co-formulants.

The CompTox dashboard provides information on the substance EDC properties in its summary section. However, in most cases, it will simply indicate "No endocrine disruption relevant data available". When this happens, a literature search is the final option. There is no agreed search engine for this yet, and the result can be different findings.

Based on the summaries of found articles, an expert statement is needed for each co-formulant on its EDC properties. This step requires a wide range of specialist knowledge, and the conclusion can be debatable.

Possibilities for improvement

The stepwise approach shines a first light on the "dark path" of EDC assessment of co-formulants. Some improvements can, however, be made to make the path brighter.

Environmental classification is not yet included in the screening of the CLP notification database. Strong evidence has shown that endocrine disruptors can interfere with developmental and reproductive processes in wildlife, such as fish, birds and frogs. These endpoints are not yet addressed in the current chemical safety assessment but can improve an EDC assessment. Some of the available ecotoxicity studies, such as OECD TG 210 and OECD TG 229, include reproduction and morphological changes, and they may suggest endocrine disrupting impact.

Therefore, a CLP inventory screening with environmental classifications including the following are considered relevant:

- chronic cat 1;
- chronic cat 2;
- chronic cat 3; and
- chronic cat 4.

The screening of these classifications is expected to improve when new (eco)toxicity testing guidelines for EDC identification are released and make more data available.

Conclusion

The legislative requirements for assessing EDCs have increased in the past two decades. A harmonised approach for evaluating co-formulants is in development but still far from concrete. The CLP inventory's screening and literature search provide the greatest challenges. Improvement, involving multiple stakeholders, is needed because the workload of the so-called 'screening' for EDC properties co-formulants can be significant.

The views expressed in this article are those of the authors and are not necessarily shared by Chemical Watch.

Searching the literature

In any review of the literature, attention should be given to the chosen search engine. For instance, PubMed focuses on biomedical articles, while Web of Science covers a much wider field. In addition, an accurate and efficient searching approach should be developed. Neither Cas nor EC numbers are likely to present in academic reports. Therefore, current searching is done by name. Unfortunately, most co-formulants have multiple names, including trade names, chemical names, and regulatory process names, making the results highly dependent on the searched names.

Another problem is that many irrelevant articles may show up. For example, methanol as a common solvent is involved in thousands of studies. It is impossible to filter the studies on its EDC properties out of all other studies. In this case, all literature must be manually sorted based on title and abstract – an enormous workload. Alternatively, a model needs to be built for automatically sorting these articles.

If literature search remains a crucial step in the EDC identification process, an EDC properties literature database may be necessary to filter substances via unique identifiers, such as a substance's Cas or EC number.