Simplifying the Assessment of Aromatic Chemicals

The benefits of working smarter, not harder.

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"Working hard and working smart sometimes can be two different things."

—Byron Dorgan

Some advances in science and technology can help us do things quicker and smarter. We can save time and money, two precious commodities, by using our brains, computer programs and effective ways of looking at data. Let's examine two examples, one using a simplified molecular-input line-entry system (SMILES) notation as an entry to predicting chemical properties using computer programs, and the other using a new decision tree approach to establish the safety or aroma chemicals.

Those developing the new chemicals that are the engines of new technologies can gain valuable insights early in the process.

The key assumption in using computer models is in the validity of structure-activity relationships (SAR). We can compare a molecule that we don't know about to a similar one with extensive data. We can also identify a structural group we know is otherwise present in a problem molecule. We know how to design for biodegradation, for example, by having oxygen or an ester linkage built into the structure. Any relationship between a known molecule and an unknown one can provide valuable guidance.

Readily Available Tools

A tool exists which allows users to predict many critical properties of a molecule that has never been made, and it is free from the U.S. Environmental Protection Agency (EPA). Going back 20 years, computer programs have been available to calculate various properties of molecules, and the EPA has developed separate modules on areas, such as ecological toxicity and dermal permeability. All these programs have been conveniently merged into the EPI (Estimated Programs Interface) Suite.[a]

Input Conventions

The chemical name, CAS number and SMILES notation are required to input a chemical into the EPI Suite. SMILES is just a convention for transforming a chemical structure into a form that can be typed on a key pad. SMILES notation for common chemicals can readily be found by searching the Internet. For a new molecule, there are rules to follow. A simple example is to use upper case for aliphatics, lower case for aromatics and a number for the beginning and end of a ring. Thus, bromobenzene becomes c1ccccc1Br. For propylene glycol, the CAS number is 57-55-6 and SMILES is OCC(O)C.

Put that information into the EPI Suite, hit "Calculate" and go to "All Results" and pages of data will appear, which can be converted to Word by hitting a button. The Henry's law constant might seem a bit exotic, but you can find estimates of solubility, biodegradation, bioaccumulation and atmospheric oxidation, among other things. If you do the same thing with a new molecule, it will give you a big jump on predicting its physical, toxicological and ecological profile.

Applying the Technology to Fragrance

A complete dossier of testing can be done on a fragrance molecule for about $1 million. There are more than 3,000 materials in the Research Institute for Fragrance Materials (RIFM) database, so a direct assault on data acquisition would cost more than $3 billion. There must be a better way.

Since the industry cannot test on animals, alternates are a given. What is needed is an approach that is quicker, less expensive and scientifically beyond reproach. RIFM has just brought this up to date in its new criteria document, with the broad outline launched in a webinar.[b] The basic ideas behind the RIFM approach are easy enough for a layman to understand because they embrace a common-sense approach to the subject. Some key concepts are endpoint, decision tree, read-across, in silico and TTC (threshold of toxicological concern).

[a] *www.epa.gov/oppt/exposure/pubs/episuitedl.htm*

[b] RIFM Webinar, Assessing the Safety of Fragrance Materials: What are the Criteria? Dec 17, 2014

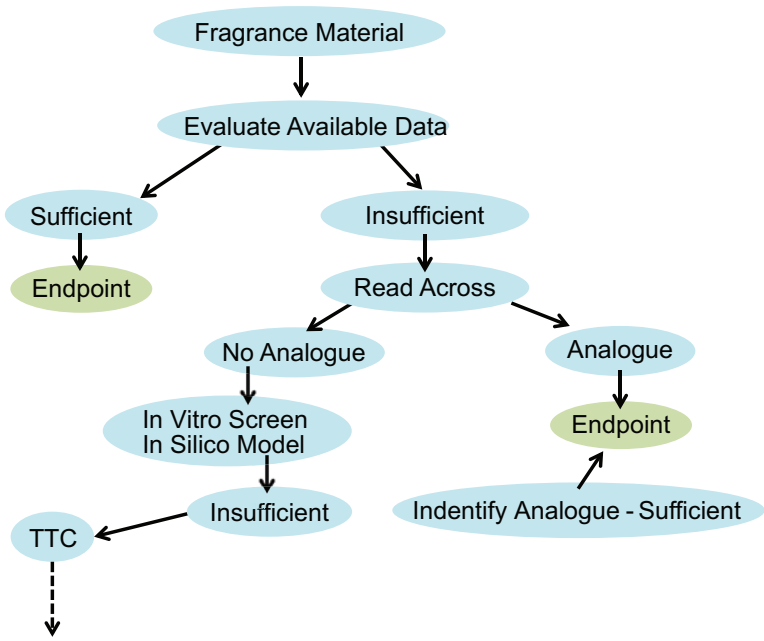
Entering a New Fragrance Material to the System

An endpoint is the place where a decision is reached on the safety of an ingredient. Endpoints that are established by RIFM for a fragrance material include genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, skin sensitization, photoirritation and photoallergenicity, local respiratory toxicity, and environmental endpoint assessment.

A decision tree: A decision tree, which leads to the endpoint, is a series of questions which serves as a road map through the evaluation process. **F-1** has a partial simplified decision tree for the beginning of a fragrance material assessment. At every juncture a question is posed, and either a decision is possible, ending the assessment, or another step is taken.

Read-across: It is first necessary to evaluate the existing data. If there is enough, the task is done. If not, the next step is to "read across"—asking if the new material is similar to another known molecule. If it is similar and there is adequate data on the known molecule, the task is done.

F-1. Fragrance assessment decision tree



In silico: The next step involves in vitro screens or in silico methods using predictive toxicology programs. In silico is a general term for the use of computer programs rather than experimental work. For toxicology studies, RIFM has access to Derek, MultiCASE, Topcat and the OECD Toolbox. If this proves sufficient, this is the endpoint. If not, the next step is to proceed to the TTC.

TTC: The TTC has been developed to handle the thousands of chemicals that can now be identified in minute quantities, virtually anywhere. It originated in 1995 in work by the U.S. FDA for food products and additives. TTC calculates a safe level, even for most carcinogens present in all food ingested over a lifetime. Certain categories, like heavy metals and endocrine disrupters, are excluded.

Natural products are an example of compounds that cannot be characterized completely, so TTC is a useful approach to handling all the pesky little chemicals present. No chemical reaction runs to 100%, so every synthesized chemical used by the industry has tiny by-products. A way was desperately needed to deal with all these materials, and TTC is the answer.

Fundamentally, TTC is an approach for prioritizing the assessment of chemicals with low-level exposures. Three broad categories of materials have been identified and are shown in **F-2**. The permitted exposure levels for each group are based on the decision tree work of Cramer, as follows:

- Cramer Group I: 1800 µg/day
- Cramer Group II: 540 µg/day
- Cramer Group II: 90 µg/day

F-2. Cramer classification scheme

- Class I Substances with simple chemical structures and for which efficient modes of metabolism exist, suggesting a low order of oral toxicity.
- Class II Substances which possess structures that are less innocuous than class I substances, but do not contain structural features suggestive of toxicity like those substances in class III.
- Class III Substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups.

Conclusions

Tools like EPI Suite and decision trees such as those used by RIFM make the industry's work more efficient, cut the time and costs of development or assessment, and allow for better predictions of the safety and performance of ingredients. In a world that demands safety to humans and the environment, they cannot be ignored. And to those developing the new chemicals that are the engines of new technologies, the insight they can gain early in the process is invaluable.

Anyone who questions the industry's commitment to safety should examine the fragrance endpoints in the decision tree. Hardly anything in contemporary society, with the exception of drugs, is so rigorously examined, with the results published by an expert panel in peer-reviewed journals, and compliance expected by all industry stakeholders. There is no rational reason to doubt the industry's intention to produce the safest fragrances based on the soundest science.

References

1. G Cramer et al., "Estimation of toxic hazard—a decision tree approach. *Food Cosmet Toxicol*, **16**, 255–276 (1978)