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Viewpoint

Current frameworks for environmental and health assessment of hydrocarbon streams and products are flexible and ready for alternative non crude oil-based feeds

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Hazard and risk assessment of complex petroleum-derived substances has been in a state of continuous improvement since the 1970s, with the development of approaches that continue to be applied and refined. Alternative feeds are defined here as those coming into a refinery or chemical plant that are not hydrocarbons from oil and gas extraction such as biologically derived oils, pyrolysis oil from biomass or other, and recycled materials. These feeds are increasingly being used for production of liquid hydrocarbon streams, and hence, there is a need to assess these alternatives, subsequent manufacturing and refining processes and end products for potential risk to humans and the environment. Here we propose a tiered, problem formulation-driven framework for assessing the safety of hydrocarbon streams and products derived from alternative feedstocks in use. The scope of this work is only focused on petrochemical safety assessment, though the principles may be applicable to other chemistries. The framework integrates combinations of analytical chemistry, *in silico* and *in vitro* tools, and targeted testing together with conservative assumptions/approaches to leverage existing health, environmental, and exposure data, where applicable. The framework enables the identification of scenarios where *de novo* hazard and/or exposure assessments may be needed and incorporates tiered approaches to do so. It can be applied to enable decisions efficiently and transparently and can encompass a wide range of compositional space in both feedstocks and finished products, with the objective of ensuring safety in manufacturing and use.

Key words: UVCBs; biofeeds; alternative feeds; complex mixtures; risk assessment methods.

Introduction

Crude oil, and crude-derived hydrocarbon products are categorized as substances of unknown or variable composition, complex reaction products and biological materials (UVCBs).[1] Many UVCB substances are manufactured at refineries and chemical plants which use a variety of physical (separation) and chemical (conversion) processes to meet defined performance specifications based on final product composition and properties. Refinery and chemical plant operations require continual optimization of processes and outputs, balancing dynamic crude oil sources with market factors. Accordingly, industry has developed innovative approaches to characterize the environmental/health hazards and manage risks for UVCBs. These include the establishment of the PETROTOX and PETRORISK tools for environmental hazard and risk assessment of petroleum streams;[2,3] the IP346 and ASTM E1687 Modified Ames screening methods to determine the carcinogenic potential of lubricant base stocks;[4,5] and the substance grouping strategies based on product/stream type and health and environmental effects utilized to test and evaluate broad categories of petroleum substances for the United States Environmental Protection Agency (EPA) and the Organization for Economic Co-operation and Development (OECD) High Production Volume Programs.[6] As the science continues to evolve, so do risk assessment approaches.

With growing demand for lower emission and more circular products, new non-crude oil feedstocks (i.e. alternative feeds) are increasingly being utilized to manufacture hydrocarbon products and streams. For the purpose of this paper, alternative feeds encompass any material which is not directly derived from crude oil, that can be used to manufacture hydrocarbon products through processes similar or equivalent to those currently employed in petroleum refineries. Examples include waste polymers that are used in chemical recycling, used cooking oil (UCO), vegetable or seed oils, and pyrolysis oils of different origin (e.g. waste polymers, biomass). Alternative streams include intermediate refinery streams and/or finished products that are derived partly or wholly from alternative feeds. Table S1 in the Supplemental Material describes some hydrocarbon refinery processes, options for how to introduce alternative feeds, and considerations from the health and environmental risk assessment perspective. In an evolving scientific landscape, our goal is to provide a framework for maximally use of the existing rich dataset on hydrocarbon substances, and flexibly integrating

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modern approaches which continue to evolve to identify and then address potential data gaps to ensure new products can be used safely. Consequently, we aim to demonstrate the readiness of this framework to assess health and environmental risks. Data and conclusions generated could be used to inform impact assessment,[7] however herein we only focus on petrochemical risk assessment. Future work aims to test and employ this framework on case studies using alternative feed samples.

Addressing questions of similarity between alternative versus virgin petroleum-derived feeds/streams/products

For complex hydrocarbon products such as solvents, fuels and asphalt, there are established and well-characterized means to conduct hazard and risk assessment.[8–14] The understanding of petroleum product toxicity has been established through extensive data generation programs[6,13,15,16] which have led to the following fundamental conclusions that continue to be applied and refined as needed[9]:

- Hydrocarbon products are complex, but through similarities in source, composition, and manufacturing processes, enable them to be grouped together to facilitate assessment.
- For human health assessment, there are particular constituents that may cause toxicity by specific modes of action, with the rest exerting baseline toxicity.
- For environmental assessment, the overwhelming mode of action of hydrocarbon toxicity is baseline toxicity.[17]

The above statements enable hazard and risk assessment of current products, typically leveraging compositional information. However, the introduction of new products which may include constituents that were not part of historic data generation requires further analysis. Whether the above statements apply to alternative feeds depends on a critical determination: How similar is similar *enough*?

We describe here a tiered framework to facilitate answering this question. The framework here adapts elements of several next generation risk assessment schemes, including those presented by Embry et al.,[18] Thomas et al.,[19] and in particular Andersen et al.[20] in order to comprehend the latest advancements in science, enabling fit for risk decisions to be made while minimizing unnecessary animal testing. We have further adapted these schemes to address key considerations for complex and variable substances derived from alternative feeds and streams. Specifically, special considerations are made related to understanding the compositional properties and variability of the alternative feed-derived substance to enable integration into hazard and exposure assessment. We do not recommend specific analytical methods in this work. The methods will vary in complexity depending on the stream and the amount of data needed to determine similarity. Ultimately, it is founded on the continued principle that complex and variable hydrocarbon substances of any source require an adaptable, tiered approach to hazard and risk assessment, and that decisions should be informed by a risk evaluation. For a detailed list of example health and environmental frameworks used for assessing petroleum streams and products, see the additional references in Supplemental Material.

Figure S1 depicts the approach to hazard and risk-assessing hydrocarbons derived from conventional feedstocks and contrasts it with the proposed approach that leverages many of the same tools and approaches, but incorporates a tiered hazard/exposure assessment approach to make data-driven decisions on testing for the purposes of safety assessment. While being discussed here primarily for alternative feeds, the tiered approach could equally be useful for conventional feeds whose differences/unknowns exceed "allowable" levels based on the suite of approaches mentioned above.

Problem formulation and initial data gathering

Assessments begin with gathering all available information to understand feedstock starting materials, intermediates, and final products. To prevent adverse impacts to the refinery (e.g. catalyst fouling, metal corrosion), as well as to ensure finished products will routinely meet product performance specifications, analytical specifications are established for feedstocks and finished products. These are typically based on performance and quality metrics and provide operational boundaries, which correlate to compositional boundaries. These are the starting points for health and environmental assessments. Through analytical characterization of lab, pilot and plant-scale manufactured products together with modeling, sufficient compositional data can be ascertained to determine to what extent the alternative product aligns compositionally to the existing health, environmental and exposure datasets (e.g.[1–3]). Generally, this requires an understanding of which constituents are present and their relative proportion of the feed including: constituent distribution by chemical class (e.g. paraffinic, isoparaffinic, olefinic, naphthenic, aromatic [PIONA] analysis) and carbon number, non-hydrocarbon impurities and an assessment of any uncertainties regarding the understanding of the composition (e.g. [6,21,22]). Key data provided by these assessments include possible presence of known hazardous components that could exceed existing boundaries as well as novel constituents/constituent classes or novel combinations of constituents. Additionally, the assessor will consider any uncertainties that would stem from knowledge about the degree of compositional variability and the representativeness of a given sample/analysis. Taken together, a determination is made as to whether sufficient information exists to proceed with the assessment, or to gather more compositional data. This may entail more detailed chemical analyses, or evaluation of composition over time to decrease uncertainty regarding expected boundaries within which the composition may fluctuate. Overall, initial data gathering thoroughly addresses potential known and unknown constituents of feed composition, which are then further assessed from the health and environmental standpoint as described below.

What follows in Fig. 1 is an iterative, tiered approach to assessment and data gathering that focuses on aspects of hazard/toxicity (specifically bioactivity, persistence, bioaccumulation) and exposure, with progression to the next tier based on the understanding and mitigation of potential risk. In all tiers, a risk characterization is conducted where a hazard point of departure is compared with predicted exposures across all uses in the lifecycle to determine the margins of exposure (MoE), the ratio of the estimated toxic effect level and estimated exposure; therefore, a lower MoE indicates higher potential risk.[23] The MoE is a decision point that could trigger progression to higher tiers to refine hazard and/or exposure assessment, or also to implement risk management measures to decrease potential exposure. Acceptable MoEs for a particular case should be clearly defined in the problem formulation and may depend on the particular use/scale (lab/pilot plant versus commercial). How one progresses to higher tiers should be

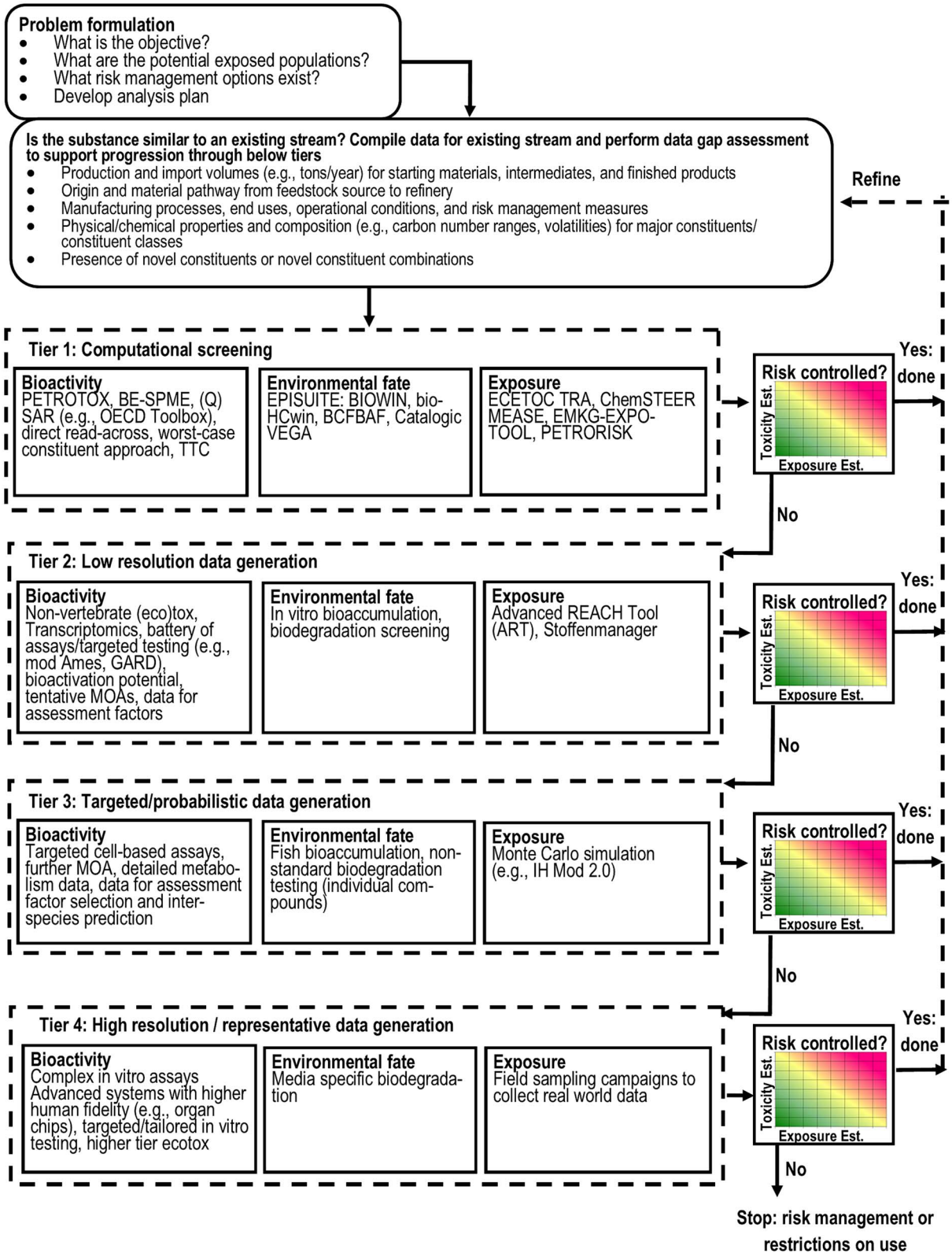

Fig. 1. Illustrative flow diagram of the framework for tiered assessment of hazard and exposure for an alternative feed/stream under consideration. Progression through tier levels proceeds from generalized, screening level assessments to increasingly detailed and representative data generation. Generally, further refined assessment is needed when the lowest tier level does not provide adequate confidence to support decision making or if the margin of exposure (MoE) is exceeded. Example assessment approaches and tools are provided at each tier. It should be noted that these suggested tools should not be considered an endorsement of or an inclusive list of all current tools; nor should they be considered exclusive of employing new tools or methods in the future. At each step, whether or not and how to proceed is guided by the RISK21 framework principle of co-visualizing hazard and exposure relative contributions to risk.[18] The small inset figures demonstrating co-visualization of hazard and exposure data were generated with the HESI RISK21 webtool.[36]

influenced by where data would be most impactful in better characterizing risk and decreasing uncertainty. The RISK21 framework developed by Embry et al. provides a practical tool to visualize both assessments' contributions to risk and identification of which, with refinement, provides the most opportunity for risk reduction.[18] Furthermore, in consideration of worker protection, it should be noted that workplaces are regulated under national authorities to comply with relevant occupational exposure limits (OELs).[24] There are also voluntary guidance documents which implement more protective OELs, such as the American Conference of Government Industrial Hygienists (ACGIH®) Threshold Limit Values (TLVs), or internally developed limits, such as in the case where there is new scientific evidence or no regulatory limits exist for a specific substance.[24,25] These values are used to inform selection of site-specific risk management measures.

Feeding data into tiered assessment of hazard and exposure

Returning to the question posed above regarding similarity between alternative versus virgin petroleum-derived feeds, both exposure and hazard assessment must be considered. Substances with different physiochemical properties may have increased or decreased likelihoods of exposure regardless of relatively different levels of hazard.[26] In the initial data gathering phase, emphasis for exposure assessment is on substance production/importation volumes, physical/chemical properties impacting physical form and therefore potential exposure route(s) (i.e. volatilities for liquids or aerosolization of solids as dust), and tasks/uses by workers and consumers, including risk management measures, frequencies/durations, and conditions of use.[27] The collection of this exposure relevant data poses challenges and opportunities for methodological development, such as has been demonstrated under the European Union's REACH.[27–29]

Using a tiered approach, exposure assessment progresses from high throughput, conservative, screening level modelling strategies to further refined assessments incorporating more details and real-world data.[30,31] Increased complexity and refinement will reduce uncertainty and more accurately characterize exposure variability; however, it also requires more resources. In the final tier of assessment, field sampling campaigns may be conducted to generate real world data such as by conducting exposure monitoring. Which exact type of data to collect as appropriate will be guided by the initial problem scoping and objectives and should be fit for purpose given the substance/scenario under consideration.

Hazard assessment can be pursued by two generally different approaches, with significant overlap. Specifically, based on an assessment of the information gathered in the initial data gathering phase, the assessor may choose to pursue either 1) a read-across approach or 2) a *de novo* risk assessment, in which anchoring to read-across may be a lesser factor and new substance toxicological and environmental data are generated. A choice of one path versus another is not mutually exclusive, and the approach can be changed upon further data analysis or new data generation. However, in general, both methods rely on similar tools and assessment approaches, from *in silico*, to *in vitro* and *in vivo*. The first relies on the use of, and potential gathering of evidence to support chemical and/or biological similarity. In initial tiers, the approach focuses on grouping of substances together with those with defined hazard and risk, as more commonly used in human health assessment[6,8] or those with similar compositions as more commonly used in environmental assessment.[3,32,33]

Grouping may be for the purposes of defining equivalent substances, or it may also be to define worst-case analogs for read-across, where the conclusion would be that the substance being evaluated is no worse than the analog(s). Such conclusions may be based on compositional data, but depending on certain concerns identified in initial tiers, further information (both analytical and biological) may be generated to test and substantiate such determinations. These data can be gathered using increasingly complex methods such as those indicated in each tier of Fig. 1. It should also be noted that the suggestions found in Fig. 1 should not be considered inclusive of all current tools, nor should they be considered exclusive of employing new tools or methods in the future.

The second approach (*de novo* risk assessment) would be to make decisions independent of the existing dataset for complex hydrocarbon substances. This could be applied if compositional analysis indicates the substance is different or novel. In initial tiers, such approaches may include utilizing the threshold of toxicological concern[34] or basing decisions on risk assessment of reasonable worst-case constituents. The use of select testing to identify potential modes of action for adverse effects and increasingly targeted approaches at higher tiers to narrow on modes of action and determine specific points of departure for risk assessment is also considered. This type of approach, which falls into a broader category of "next generation risk assessment" approaches is an area of rapid evolution.

This framework is scalable and flexible in a manner where ultimately, *in vitro* approaches could also be applied, through *in vitro* to *in vivo* extrapolation, to derive equivalent administered doses (EADs) for subsequent risk characterization.[35] If the last tiered assessment is performed and the result is still that risk is not controlled, then final actions include further implementation of additional risk management measures, such as personnel protective equipment for workers, alternations to product formulations and/or gathering of additional data to refine the assessment. Ultimately, if it is deemed not possible to control risk, then that substance/use combination will not be supported.

Summary

Given the variable nature of petroleum UVCBs and their crude feedstocks, the health and environmental risk assessment frameworks developed to address these substances demonstrate adaptability by necessity and design. Therefore, under the increasing demands for alternative feeds, streams, and products, we postulate that these frameworks are ready to address these challenges or further evolve as needed. Past frameworks focused on UVCBs have been combined and extended specifically to develop the framework presented here.[18–20] Key points of assessment include: 1) determination of how similar an alternative is compared to the original feed/stream/product, and 2) gathering necessary substance identity and background data and 3) progressing through a tiered risk assessment framework. Ultimately, the framework presented here illustrates a ready and time-tested process for evaluating the environmental and health risks associated with forthcoming alternative feeds, streams, and products. Future work will aim to test this framework by case studies.

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Supplementary material

Supplementary material is available at *TOXRES Journal* online.

Conflict of interest statement

The authors are employees of ExxonMobil who provided funding for this study via ExxonMobil Biomedical Sciences Inc. (EMBSI), a wholly owned subsidiary of ExxonMobil Corporation.

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