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Mary S. Wolfe, Ph.D.
Deputy Director for Policy
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Re: US Strategic Roadmap: New Approaches to the Principles and Practice of Validation; OECD activities to increase the utility and uptake of AOPs in regulatory contexts across countries

Dear Members of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM):

The American Petroleum Institute (API) is pleased to provide written comments regarding OECD activities to increase the utility and update of adverse outcome pathways (AOPs) in regulatory contexts across countries. API also intends to provide oral comment at the 19-20 September 2019 SACATM meeting. API is a national trade association that represents all facets of the oil and natural gas industry, with 600 plus members that include large integrated companies, as well as exploration and production, refining, marketing, pipeline and marine businesses, and service and supply firms. As a core component of our business model, we prioritize the promotion of public health and environmental safety while ensuring a strong, viable and sustainable US oil and natural gas economy. API advocates for risk assessment processes that use the best available science, are transparent, and provide opportunities for public engagement.

API has been an active stakeholder in US EPA's efforts to develop and implement new approach methodologies (NAMs)[1][2][3] as directed under the Lautenberg Chemical Safety Act (LCSA). API anticipates that the mandates of the revised TSCA to reduce animal testing will be a strong driver for development of alternative toxicological methods throughout EPA agency-wide. API is also aware of a very recent Memorandum from Administrator Wheeler committing EPA to reduce requests/funding of animal studies 30%

[1] API public comment on Alternative Test Methods and Strategies to Reduce Vertebrate Animal Testing. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2017-0559-0543
[2] API public comment on EPA's March 7, 2018 Draft Strategic Plan to Promote the Development and Implementation of Alternative Test Methods. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2017-0559-0591
[3] API Public comment on EPA's April 4, 2018 Draft Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing. https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0093-0162

by 2025 with complete elimination by 2035 unless approved by the Administrator on a case-by-case basis[4]. Additionally, we expect EPA's adoption of NAMs to influence other federal agencies. API appreciates the valuable role of the SACATM in this process.

API considers AOPs as critical for temporal and biological integration of effects. API provides several suggestions herein for increasing the utility and uptake of AOPs by the regulatory and regulated communities.

Suggestion 1: An OECD Council recommendation on mutual acceptance of AOPs may be necessary to increase the utility and uptake of AOPs in regulatory contexts across countries. This would have added benefits of standardization, efficiency, and harmonization.

The development of AOPs, and peer review thereof, as well as the development and maintenance of AOP databases, requires substantial resources from both OECD and stakeholders. There is little incentive to continue to devote resources to developing AOPs (and to maintaining centralized databases) if there can be no assurance that agencies will accept them for regulatory use. In practice, an OECD Council recommendation for Mutual Acceptance of Data was necessary to promote regulatory acceptance of harmonized OECD Test Guidelines. From our viewpoint, this approach appears to have been largely successful. A similar recommendation may be necessary to achieve regulatory acceptance of AOPs.

A counter-argument is that a mutual acceptance recommendation from OECD for AOPs is both extreme and unnecessary because the mandated use of NAMs provides sufficient conditions for the organic development, promotion, and regulatory use of AOPs. Increasingly, regulatory frameworks are being modernized to require a transition from animals use to NAMs. This would be expected to naturally promote the use of AOPs because AOPs provide the necessary bridge between NAMs and adverse effects. Even without review by OECD or OECD's centralized database, AOPs can be still be published in the peer-reviewed literature and/or submitted to regulatory agencies during the course of regulatory review.

However, continued centralization of AOP review at OECD, together with an OCED recommendation for mutual acceptance, would have benefits that an organic approach would not. These benefits include better standardization of AOP review, more efficient use of resources (including stakeholder resources in identifying AOPs because they would be housed in centralized location), and promotion of regulatory harmonization.

Suggestion 2: AOPs based on known mechanisms of toxicity would provide a unique opportunity to increase the utility and uptake of AOPs in regulatory contexts.

[4] Memorandum from Administrator Andrew R. Wheeler to Associate Deputy Administrator, General Counsel, Assistant Administrators, Inspector General, Chief Financial Officer, Chief of Staff, Associate Administrators, Regional Administrators. Directives to Prioritize Efforts to Reduce Animal Testing. September 10, 2019.

Mechanisms of toxicity that span molecular initiating events through the manifestation of adverse effects at the level of the whole organism have been established for a number of substances. Many of these mechanisms reflect underlying biological processes culminating in toxicity that are common to more than one substance. In many cases, these known mechanisms address interspecies differences that speak to the human relevance of toxicity endpoints, which is highly relevant to regulatory decisions. Hence, the argument can be made that these mechanisms of toxicity are akin to AOPs. However, in many cases, these mechanisms may actually have a more detailed body of evidence than what would be required to substantiate an AOP. In these situations, AOPs derived from biological mechanisms, e.g., 'mechanism-derived AOPs', can be rapidly assembled from the existing evidence base.

Regulatory acceptability (e.g., 'uptake') for 'mechanism-derived AOPs' would be anticipated to be high. This is because regulators have been aware of many of these mechanisms for decades. Regulatory utility would also be expected to be high, since 'mechanism-based' AOPs already address issues critical for risk assessment and regulation, such as interspecies differences and human relevance.

Suggestion 3: 'Key characteristics' should not be equated with AOPs or used as substitutes for AOPs.

API supports the use of AOPs as a bridge between NAMs and adverse effects. API is aware of recent literature that identifies 'key characteristics' of both carcinogens[5] and reproductive toxicants[67]. At present, the use of 'key characteristics' seems to be limited to use as an organization tool in the weight-of-the-evidence and not as a stand-alone for hazard identification or classification. However, we are concerned that as the concept of 'key characteristics' expands, there will be a tendency for some users to equate them with AOPs or use them as substitutes for AOPs. As such, we wish to make this distinction clear now and to provide a reference as a caveat. A 2017 analysis by Becker *et al.* found that the ability of ToxCast/Tox21 data corresponding to mechanism-based features of carcinogens did not exceed chance for predicting classifications of carcinogenic potential by USEPA.[8] This indicates to us that 'key characteristics' should not be equated with complete AOPs or used as substitutes for AOPs.

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[5] Smith et al. Key characteristics of carcinogens as a basis for organizing data on mechanism of carcinogenesis. Env. Health Perspec.. 124(6). June 1, 2016.

[6] Luderer et al. Proposed key characteristics of female reproductive toxicants as an approach for organizing and evaluating mechanistic data in hazard assessment. Env. Health Perspec.. 127(7). July 19, 2019.

[7] Arzuaga et al. Proposed key characteristics of male reproductive toxicants as an approach for organizing and evaluating mechanistic evidence in human health hazard assessments. Env. Health Perspec.. 127(6). July 14, 2019.

[8] Becker RA[1], Dreier DA[2], Manibusan MK[3], Cox LAT[4], Simon TW[5], Bus JS[6]. How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data? Regul Toxicol Pharmacol. 2017 Nov;90:185-196. doi: 10.1016/j.yrtph.2017.08.021. Epub 2017 Sep 1.
http://www.sciencedirect.com/science/article/pii/S0273230017302714?via%3Dihub

Suggestion 4: Utilization of AOPs may be limited by the applicability domain of the NAMs used to support them. In order to maximize the use of AOPs, NAMs used to support AOPs should encompass substances with a broad range of physicochemical properties.

Some NAMs may not be suitable for all substances. To the extent that unsuitable NAMs are used to support the Key Events of an AOP, it may not be possible to use that AOP to inform regulatory decisions for these substances. US EPA recently published a science policy document for skin sensitization that used aqueous-based NAMs to support Key Events in a Defined Approach for skin sensitization testing[9]. Petroleum streams are a class of Chemical Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials (aka 'UVCB' substances) that are highly hydrophobic with low water solubility. These properties may render them incompatible with many aqueous-based NAMs and therefore outside of the applicability domain. Presently, it is unclear to API if any of the NAMs used in EPA's Defined Approach for skin sensitization testing will be compatible with petroleum streams or other, hydrophobic substances. If this proves to be the case, then *in vivo* data may be necessary.

API understands that the use of NAMs and AOPs in regulatory contexts is relatively new, that one must start somewhere, and that aqueous-based NAMs are based on technology (e.g., cell-free or cell-based assays) that have been around for decades and are relatively well understood. That said, the universe of highly hydrophobic substances extends far beyond petroleum stream UVCBs and we would anticipate similar challenges for other, highly-hydrophobic substances. As such, we encourage the SACATM to advance the development of NAMs that encompass highly hydrophobic substances in the applicability domain and to consider incorporating hydrophobic-friendly NAMs as support for AOPs.

In closing, API applauds the SACATM's efforts in engaging with OECD on increasing the utility and uptake of AOPs in regulatory settings. It is our hope that our suggestions herein may prove useful in this endeavor.

Sincerely,

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[9] Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing. April 4, 2018. https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0093-0090