Organizing mechanism-related information on chemical interactions using a framework based on the Aggregate Exposure and Adverse Outcome Pathways

Paul S. Price, PhD

U.S. EPA (retired)

Society of Toxicology Webinar

Risk Assessment and Mixtures Specialty Sections

September 9, 2020

These slides are the sole product of the author, have not been reviewed by the U.S. Environmental Protection Agency, and may not reflect the agency's policy.

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Toxicology

A proposal for creating a taxonomy of chemical interactions using concepts from the aggregate exposure and adverse outcome pathways

Paul Price[1] and Jeremy Leonard[2]

Abstract

Currently, there is no single taxonomy for organizing data on the various types of chemical interactions that may affect risks from combined exposures. A taxonomy of chemical interactions is proposed that is based on a combination of the aggregate exposure pathways (AEPs) and adverse outcome pathways (AOPs) (AEP–AOP framework). The AEP–AOP framework organizes data on the causal events that ocur over the entire source–exposure–response continuum of a chemical's release. The proposed taxonomy uses this framework in two ways. First, four top-level categories are established based on the location in the continuum where a chemical interaction occurs. Second, each top-level category has two or more subcategories that are based on concepts taken from AEPs and AOPs. The categories and subcategories are potentially useful in developing standardized definitions for interaction terms and improving our understanding of the impacts of chemical interactions on risk to human health and the environment.

Addresses

[1] National Exposure Research Lab, ORD, U.S. Environmental Protection Agency, 109 TW Alexander Drive, RTP, NC, 27711 USA

[2] Oak Ridge Institute for Science and Education, Environmental Media Assessment Group, National Center for Environmental Assessment, U.S. Environmental Protection Agency, 109 TW Alexander Drive, RTP, NC, 27711 USA

Corresponding author: Price, Paul (price.pauls@epa.gov)

Current Opinion in Toxicology 2019, **16**:58–66

This review comes from a themed issue on **Systems Toxicology**

This review comes from a themed issue on **Systems Toxicology**

Available online 30 May 2019

For a complete overview see the Issue and the Editorial

https://doi.org/10.1016/j.cotox.2019.05.007

2468-2020/Published by Elsevier B.V.

Keywords

Taxonomy, Chemical interactions, Aggregate exposure pathway (AEP), Adverse outcome pathway (AOP).

1. Introduction

Currently, there is no single framework for categorizing the diverse types of chemical interactions that affect the adverse human and ecological outcomes from chemicals. While multiple individuals and organizations have proposed methods of organizing information on the effects of combined exposures to chemicals [1–7], these approaches have not considered the entire source–exposure–response continuum. In many instances, such approaches have only addressed interactions between chemicals that produce a common adverse outcome (AO) in *in vivo* models [7] or that only address toxicological interactions in individual organisms [2]. This article offers an approach that has the potential to fill this gap.

Here, we propose a taxonomy that is based on the aggregate exposure pathway (AEP) framework [8–10] and the adverse outcome pathway (AOP) framework [11–13].[1] In this article, we argue that the combination of AEPs and AOPs (AEP–AOP) provides a useful framework for organizing the diverse types of chemical interactions into a hierarchical system of mutually exclusive categories. These categories can provide a more detailed organization of interactions that have at best only been broadly characterized in earlier approaches. In addition, the categories organize interactions into groups with common attributes. As a result, the taxonomy can aid in the understanding and management of impacts of chemical interactions on human health and the environment.

The proposed taxonomy is presented as an initial work. The concepts in this article are offered as a discussion starter, and we welcome additional ideas, modifications, and suggestions. This article begins with a brief review of relevant components of AEPs and AOPs, followed by a description of the taxonomy and a brief discussion.

2. The combined AEP–AOP framework

The AEP–AOP framework is an objective system for organizing information on events occurring along the source–exposure–response continuum (Figure 1A), using concepts from graph theory. In an AEP, chemical exposure is defined in terms of one or

[1] AEP–AOP: aggregate exposure pathway–adverse outcome pathway; KES, key event state; KTR, key transitional relationship; KE, key event; KER, key event relationship; AO, adverse outcome.

Environment International 138 (2020) 105673

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Organizing mechanism-related information on chemical interactions using a framework based on the aggregate exposure and adverse outcome pathways

Paul S. Price[a,*], Annie M. Jarabek[a], Lyle D. Burgoon[b]

[a] Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, 109 TW Alexander Drive, Research Triangle Park, NC 27711, United States

[b] Environmental Laboratory, US Army Engineer Research and Development Center, Research Triangle Park, NC, United States

ARTICLE INFO

Handling editor: Adrian Covaci

Keywords:
Chemical interactions
Mixture toxicity
Adverse outcome pathway
Aggregate exposure pathway

ABSTRACT

This paper presents a framework for organizing and accessing mechanistic data on chemical interactions. The framework is designed to support the assessment of risks from combined chemical exposures. The framework covers interactions between chemicals that occur over the entire source-to-outcome continuum including interactions that are studied in the fields of chemical transport, environmental fate, exposure assessment, dosimetry, and individual and population-based adverse outcomes. The framework proposes to organize data using a semantic triple of a chemical (subject), has impact (predicate), and a causal event on the source-to-outcome continuum of a second chemical (object). The location of the causal event on the source-to-outcome continuum and the nature of the impact are used as the basis for a taxonomy of interactions. The approach also builds on concepts from the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP). The framework proposes the linking of AEPs of multiple chemicals and the AOP networks relevant to those chemicals to form AEP-AOP networks that describe chemical interactions that cannot be characterized using AOP networks alone. Such AEP-AOP networks will aid the construction of workflows for both experimental design and the systematic review or evaluation performed in risk assessments. Finally, the framework is used to link the constructs of existing component-based approaches for mixture toxicology to specific categories in the interaction taxonomy.

1. Introduction

Toxicology, exposure science, and chemical risk assessment are in the midst of a transformation. Assessors are moving towards the use of *in vitro* assays and *in silico* predictions that provide insights on the mechanisms that cause adverse outcomes (AOs) (NRC, 2007). The methodologies driving this transformation have been referred to as New Approach Methodologies or NAMs (Pham et al., 2019; Wambaugh et al., 2019). *In vivo* toxicity data are limited to a relatively small number of substances. Because of the large, and increasing, number of chemicals in commerce it is envisioned that the majority of chemicals will be evaluated in the future using NAMs rather than data from *in vivo* models of toxicity (Kavlock et al., 2018). The benefits of NAMs are perhaps more critical to the study of the effects of chemical mixtures than the effects of single chemicals (Hernandez et al., 2019). There are more combinations of chemicals than individual chemicals and dose response for combined exposures are more complex than those for individual chemicals. Following Nelms et al. (2018) and Bopp et al. (2019), the term "chemical mixtures" is defined in this paper as an organism's or population's combined exposures to two or more chemicals, where the period of time between the exposures is sufficiently small as to allow the effects of one chemical to influence the response of the organism or population to one or more other chemicals. Chemical mixtures include intentional discrete mixtures (e.g., consumer products) and unintentional discrete mixtures (e.g., industrial effluents), and concurrent exposures to chemicals from multiple sources.

The hallmark of NAMs is to illuminate the mechanisms that determine the causal events in the source – exposure – dose – outcome continuum that describes the ability of a chemical to pose risks to humans and the environment (Cohen-Hubal et al., 2010; Hines et al.,

Abbreviations: ADME, absorption, distribution, metabolism and elimination; AEP, Aggregate Exposure Pathway; AO, Adverse Outcome; AOP, Adverse Outcome Pathway; CSM, Conceptual Site Model; ICKE, Initial Common Key Event; KE, Key Event; KER, Key Event Relationship; KES, Key Exposure State; KTR, Key Transition Rate; MIE, Molecular Initiating Event; NAM, New Approach Methodology; RDF, Resource Description Framework; TSE, Target Site Exposure; qAOP, quantitative Adverse Outcome Pathway

* Corresponding author.
E-mail address: paul_price@pipeline.com (P.S. Price).

https://doi.org/10.1016/j.envint.2020.105673
Received 12 December 2019; Received in revised form 16 March 2020; Accepted 17 March 2020
Available online 24 March 2020

Contributors

- Justin Teeguarden, Yu-Maei Tan, Steven Edwards (and others) for developing the Aggregate Exposure Pathway that made this possible
- Mark Nelms, Jane Ellen Simmons, Stephen Edwards for thoughtful analysis on Adverse Outcome Pathways and mixtures that anticipated much of this talk
- SETAC Pellston workshop on advancing the AOP framework
- Jeremy Leonard who coauthored an earlier paper on the taxonomy portion of the framework and Lyle Burgoon and Annie Jarabek for their work on the cited case studies and the sections on the application of the framework
- Encouragement and thoughtful comments from David Herr and Rory Connolly
- All errors and flaws are mine

Background

Challenge of chemical interactions, mixture toxicity, and the exposome

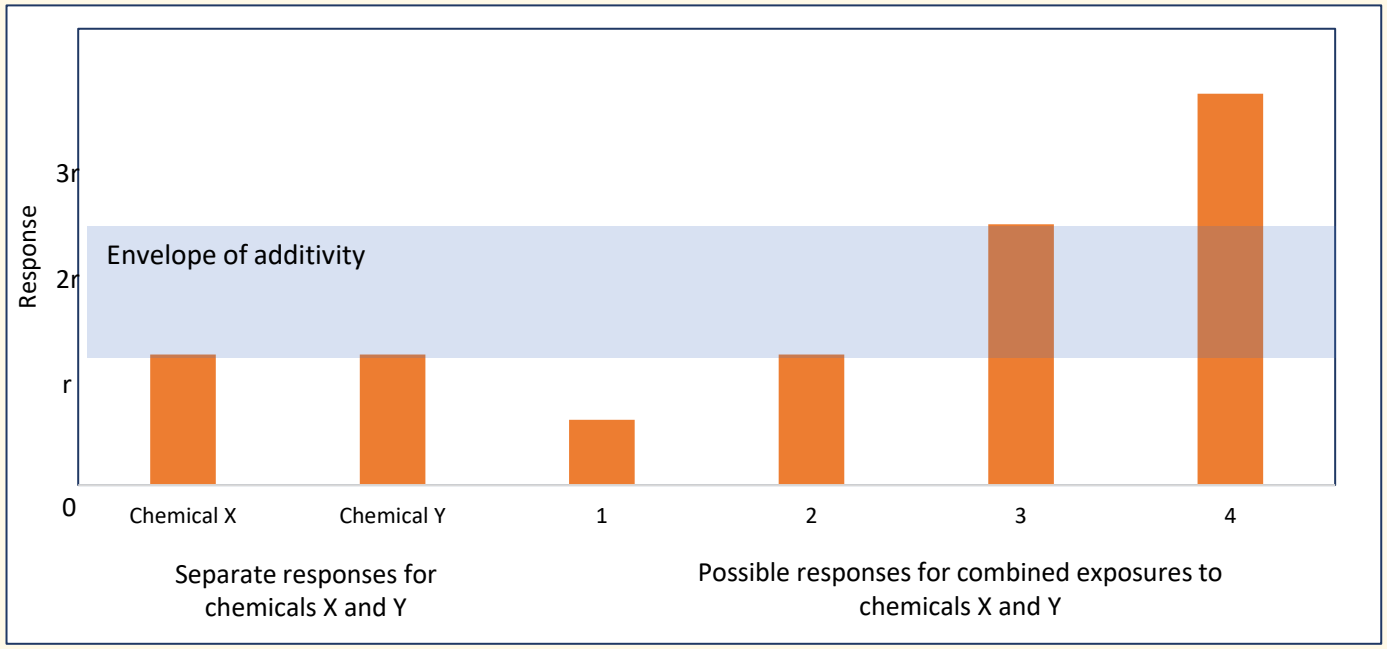
- Mixture toxicity is a function of the combinations of chemicals involved in the interaction
- The number of combinations are far larger than the number of chemicals
- Humans and ecological receptors are exposed to millions of complex mixtures
- Exposures need not be concurrent. Chemical X's effects may persist and affect the impacts of future exposures to chemical Y
- The combination of all exposure sources forms the exposome that has been shown to have significant impacts human health

Historical approaches to assessing chemical interactions in animal models

Defined by response data for groups of chemicals measured separately and together

Such data provides the basis for categories of interaction:

- Dose additivity
- Response additivity
- Synergy
- Antagonism



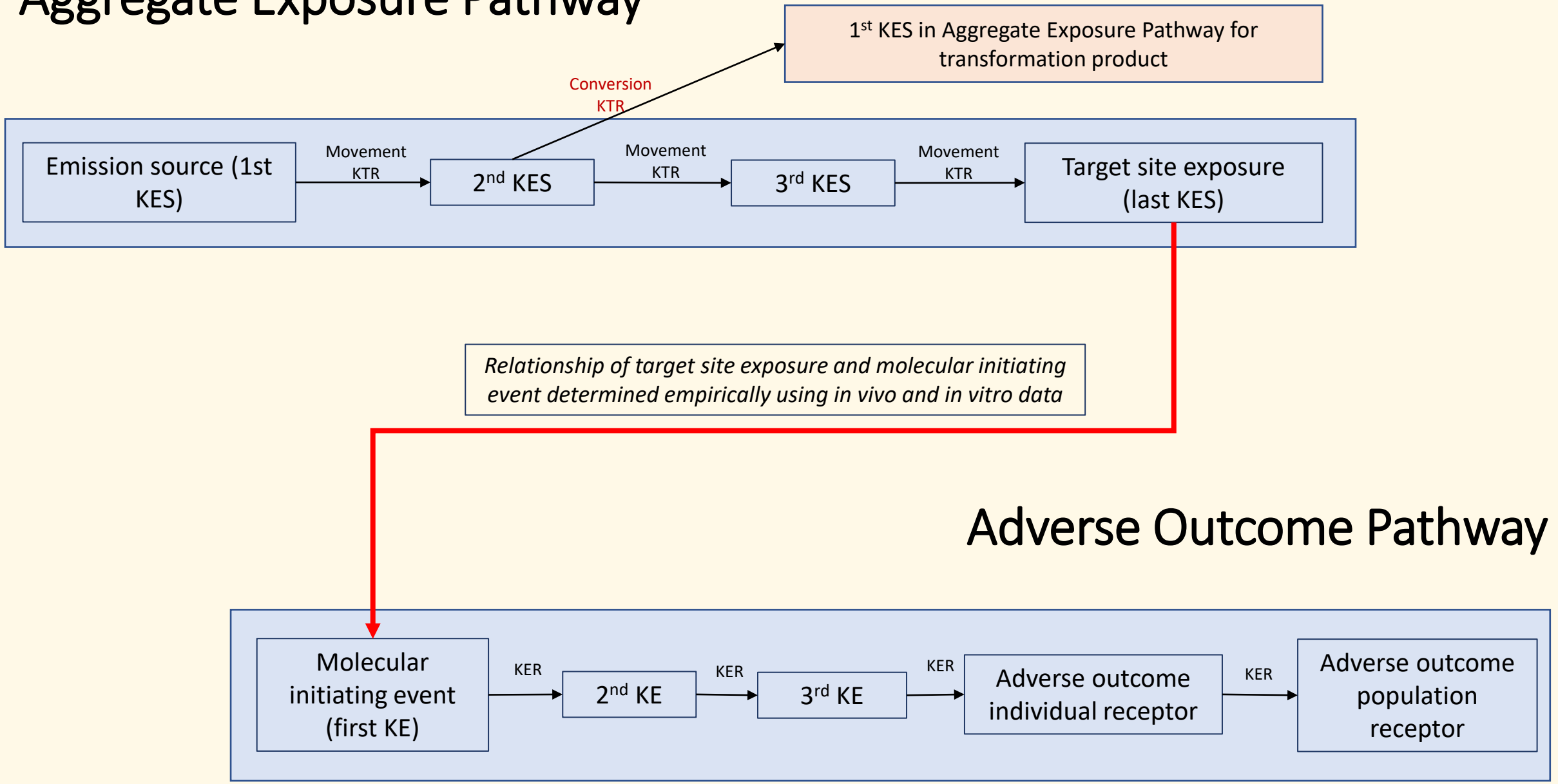
Chemical risk assessment in the 21st century and the New Assessment Methodologies

- Movement to *in vitro* and *in chemico* models of toxicity from *in vivo* models
- Leveraging *in vivo* and *in vitro* data to make *in silico* predictions
- Movement from empirical to mechanistic-based findings for toxicity, exposure, and risk analyses
- Building pipelines for high-throughput analyses
- These tools give insights on the mechanisms of toxicity but not necessarily a finding of toxicity

Adverse Outcome and Aggregate Exposure Pathways (AEP and AOP)

- Created to meet the need for flexible frameworks to organize, hold, and make use of data from existing toxicity studies, new findings, and survey results
- Based on concepts from graph theory and Resource Description Framework (RDF) approaches
- Together they cover the entire source-to-outcome continuum

Aggregate Exposure Pathway

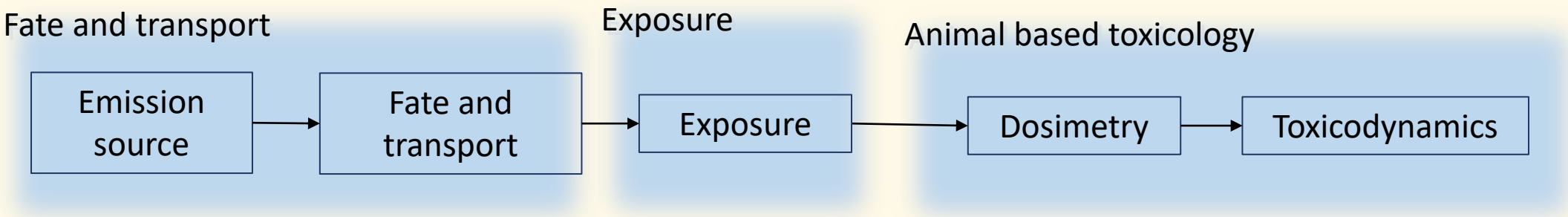


AEPs differ from AOPs

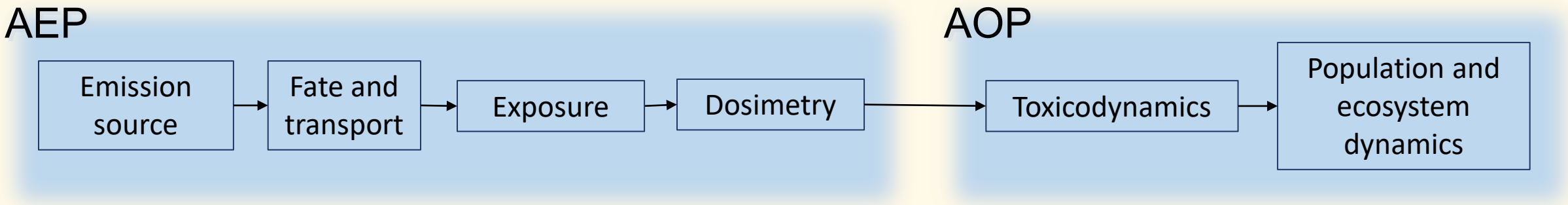
- AOPs are chemically agnostic, deal in data from multiple levels of biological organization, are time and location independent, and focus on measurable effects
- The AOPs relevant to a chemical are determined by the specific MIEs triggered by a chemical and the chemical-specific relationships between the relevant TSEs and MIEs
- AEPs are chemical-specific, deal only with mass transport and chemical reactions, and are usually time and location dependent

Dividing up the source-to-response continuum

Historical division of events by discipline



Events in a combined AEP-AOP framework



The framework

Scope of the framework

- Started with chemical interactions in *in vivo* toxicology and the AOP
- The advent of the AEP allowed the separation of toxicokinetics and toxicodynamics
- The definitions of the AEP and AOP provided the opportunity to consider interactions that occur upstream and downstream of *in vivo* toxicology
  - Release
  - Fate and transport
  - Exposure events
  - Population level and
  - Ecosystem level

Principles used in designing framework

- Start with binary interactions
- Recognize that a response in a study of combined toxicity of two chemicals can reflect multiple interactions
- Not important what the chemicals do separately
- Framework is aspirational
  - Most mixture toxicity studies do not generate the necessary mechanism data to use the framework
  - Data are not available for most chemicals
- Begin with a clear definition of what is a chemical interaction

The terms interaction and noninteraction are already defined in mixture toxicology

- Existing definitions derived from empirical data on dose and response
  - Interaction: The combined dose response cannot be explained by response addition or dose addition
  - Non interaction: The combined dose response can be explained by response addition or dose addition
- New definitions derived from mechanism
  - Interaction: The ability of one chemical (X) to cause a change in the source-to-outcome continuum of a second chemical (Y) for a defined AO
  - Non-interaction: The lack of the ability of X to cause a change the source to-outcome of Y at any dose of X below the maximum tolerated dose of X (similar to the definition of “no apparent influence”)

Interactions have direction

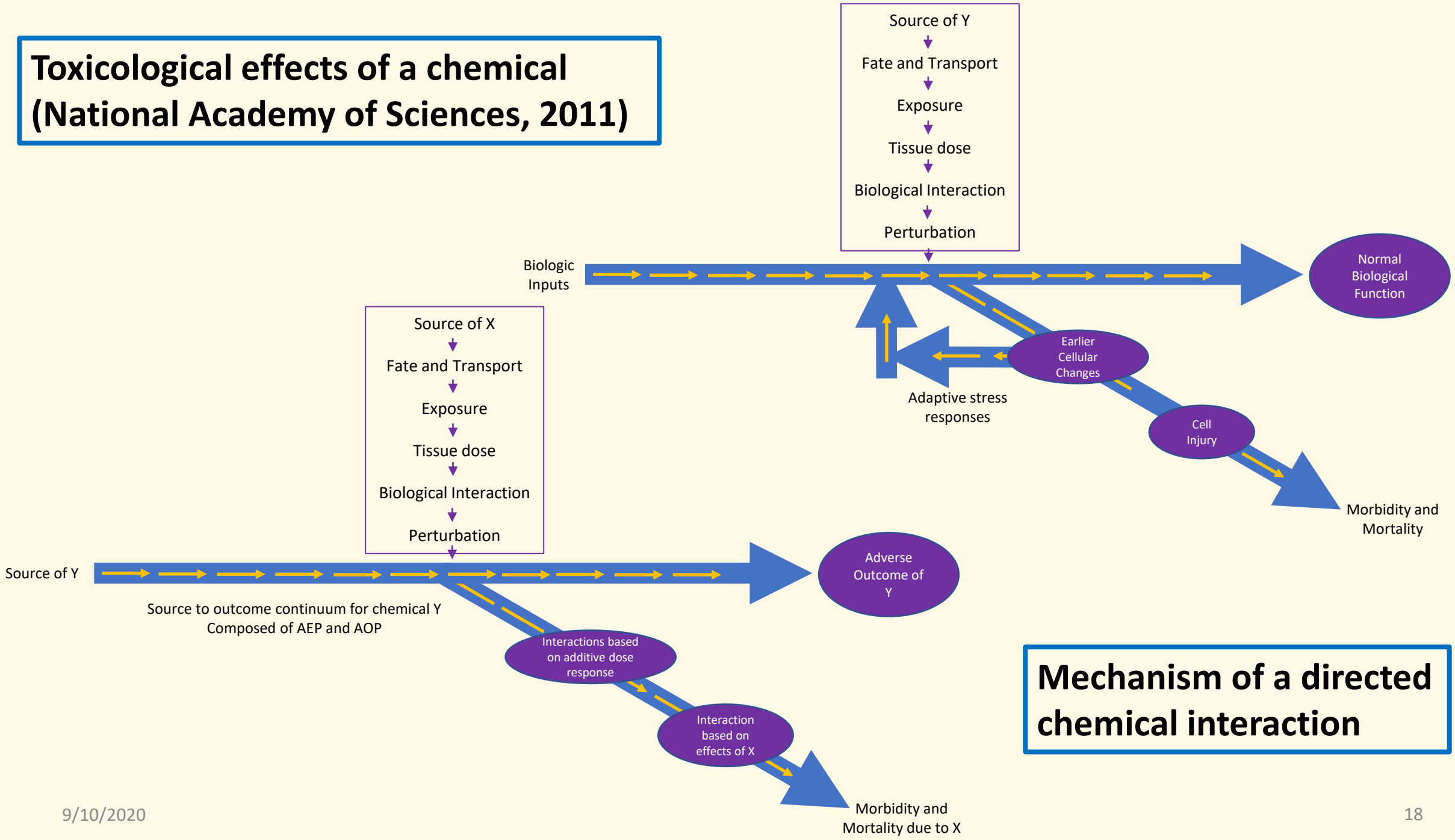
In vivo and *in vitro* models of do not indicate what chemical X is doing to the toxicity of chemical Y or what Y is doing to the toxicity X.

$$X \rightarrow Response_X$$
$$Y \rightarrow Response_Y$$
$$X + Y \rightarrow Response_{X+Y}$$

But mechanistic findings are directed - X changes the toxicity of Y by a specific mechanism

$$X \downarrow Y \rightarrow Response_Y$$

Toxicological effects of a chemical (National Academy of Sciences, 2011)



Mechanism of a directed chemical interaction

Modeling chemicals interactions in both directions

When two chemicals cause a common AO

$$X \rightarrow Response_X$$
$$Y \rightarrow Response_Y$$

It may be useful to model how chemical X changes the toxicity of chemical Y

$$\begin{array}{l} X \\ \downarrow \\ Y \rightarrow Response_Y \end{array}$$

and how chemical Y changes the toxicity of chemical X

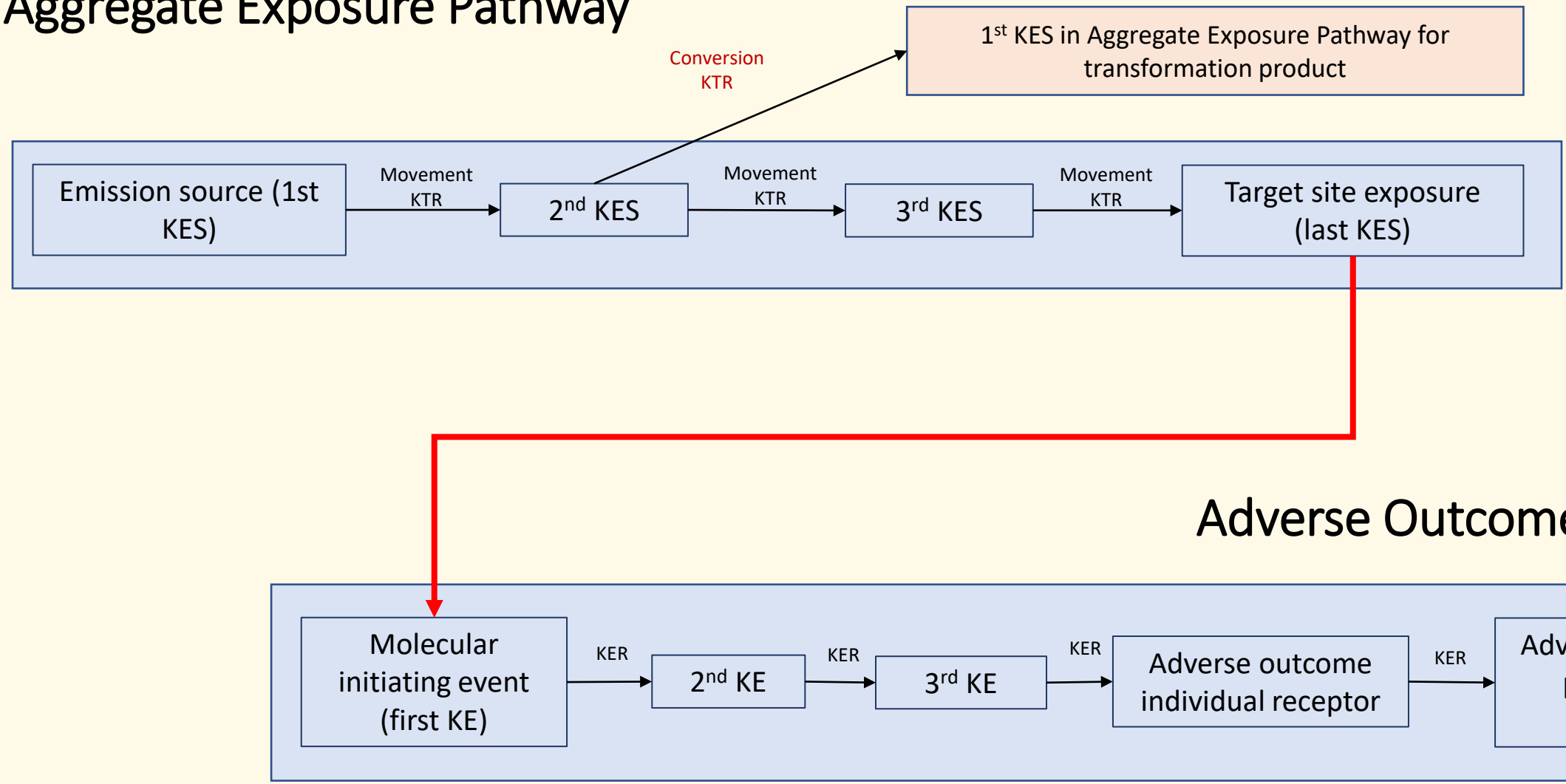
$$\begin{array}{l} Y \\ \downarrow \\ X \rightarrow Response_Y \end{array}$$

A taxonomy of chemical interactions

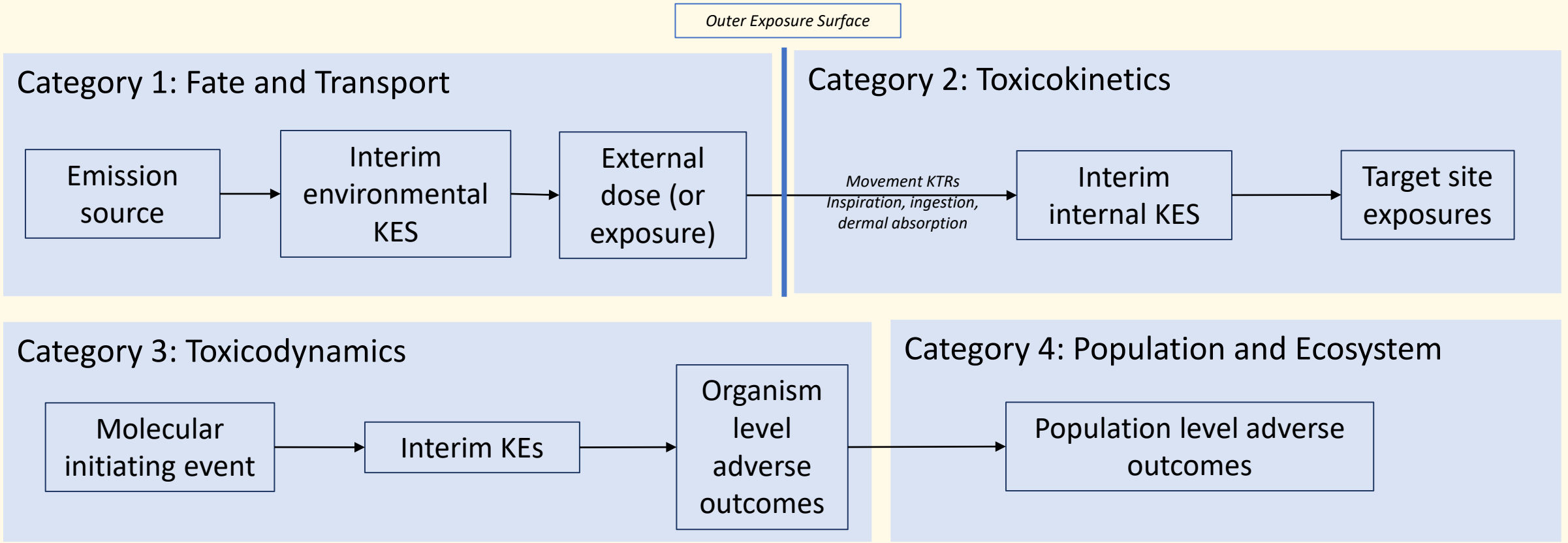
Taxonomy is offered as a useful framework for organizing findings on chemical interactions

- Covers all interactions that occur over the source-to-outcome continuum
- The system of categories are:
  - Exhaustive – all interactions fall into one of the categories
  - Mutually exclusive (an interaction will fall into only one category)
- Binary interactions

Aggregate Exposure Pathway



Top tier of taxonomy of interactions is based on location of the interaction in the continuum



Second tier of taxonomy of interactions is based on characteristics of AEP and AOP

Category 1. Interactions in release, fate, transport and exposure processes of Y

- **Category 1A. Change in the movement of Y in the environment**
- **Category 1B. Change in the conversion of Y to Y' in the environment**
- **Category 1C. Chemical reactions between X and Y in the environment**

Category 2. Interactions that change the toxicokinetics of Y

- **Category 2A. Change in the movement of Y in an organism**
- **Category 2B. Change in the conversion of Y to Y' in an organism**
- **Category 2C. Chemical reactions between X and Y in an organism**

Category 3. Chemical Interactions that involve chemicals with a common AO

- **Category 3A. Interactions involving a common MIE(s)**
- **Category 3B. Interactions involving separate MIEs but with one or more common KEs in an AOP network**
- **Category 3C. Interactions involving separate MIEs that converge to a common AO but have no other common KEs**

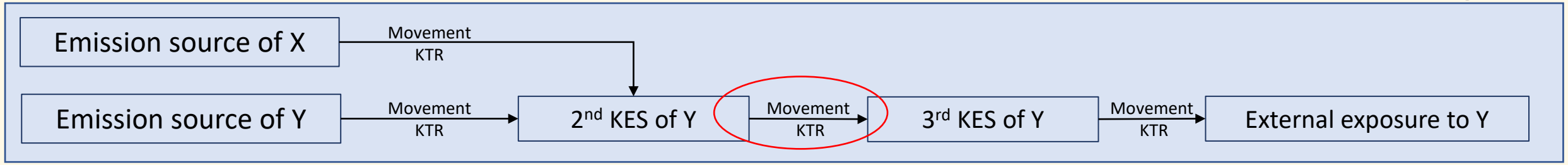
Category 4. Interactions leading to an adverse outcome in a population-based AO

- **Category 4A. Separate adverse effects affecting a common population**
- **Category 4B. Chemicals that impact a population directly and indirectly by affecting another species**

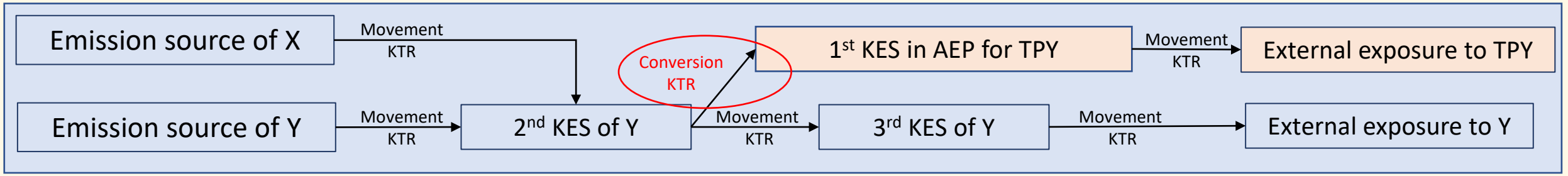
Category 1A: Interactions involving a movement KTR

AEP – Fate/ Trans./Exp.

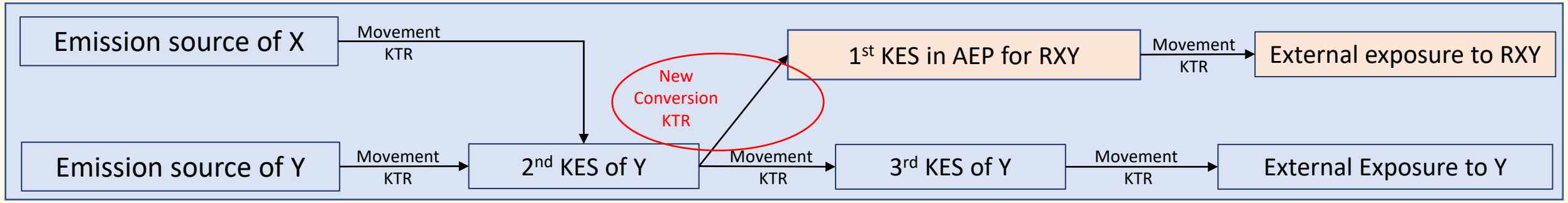
Outer Exposure Surface



Category 1B: Interactions involving a conversion KTR



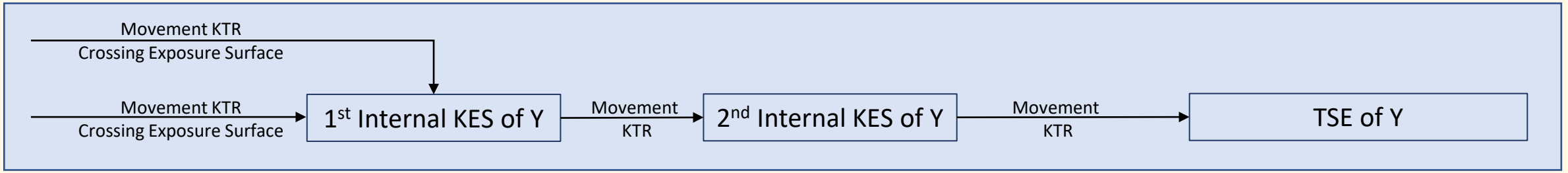
Category 1C: Interactions involving a chemical reaction



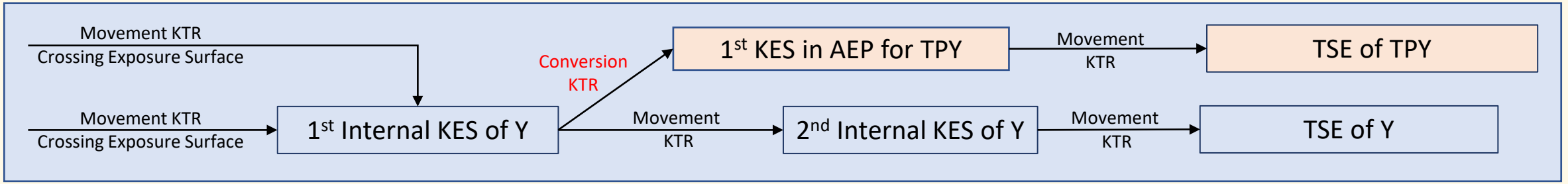
Outer Exposure Surface

AEP – Toxicokinetics

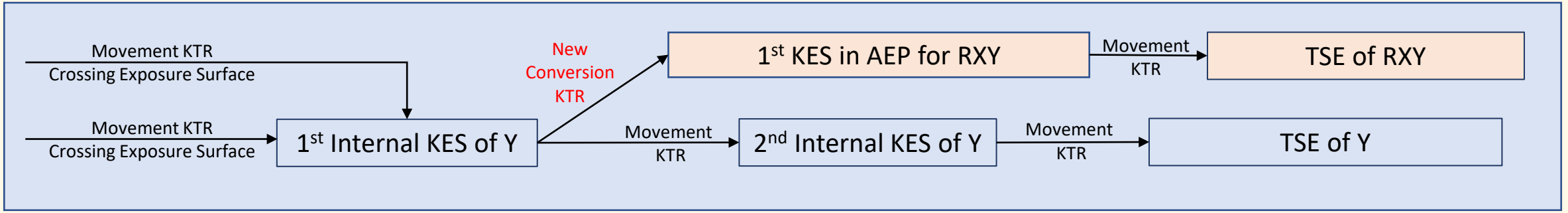
Category 2A: Interactions involving a movement KTR



Category 2B: Interactions involving a conversion KTR

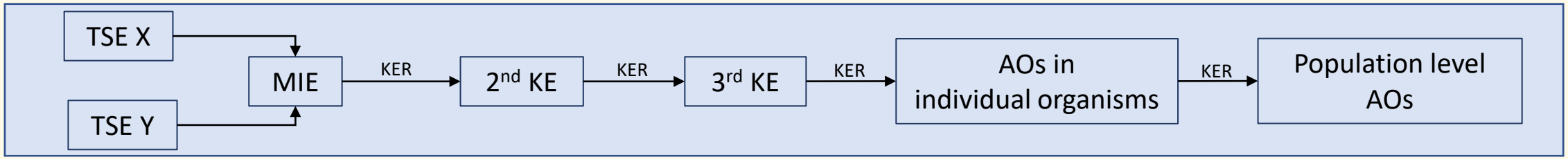


Category 2C: Interactions involving a chemical reaction

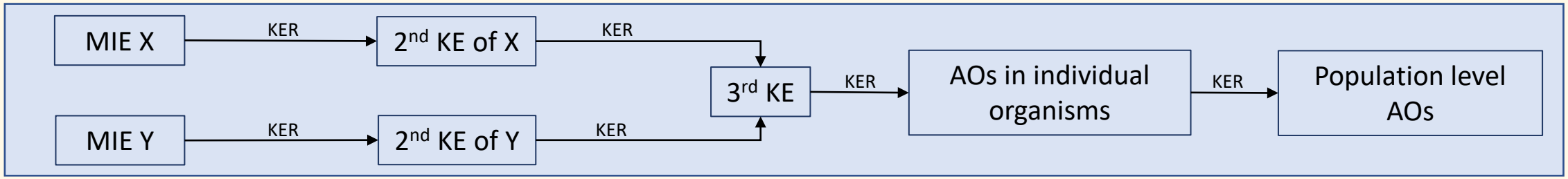


AOP – Organism level

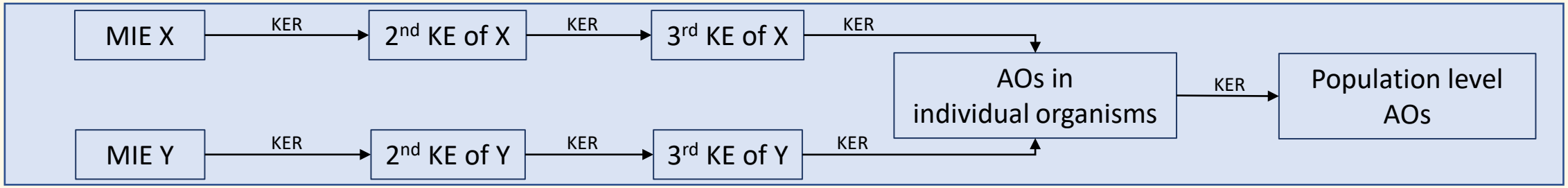
Category 3A: Interactions at a common MIE



Category 3B: Interactions at a common KE

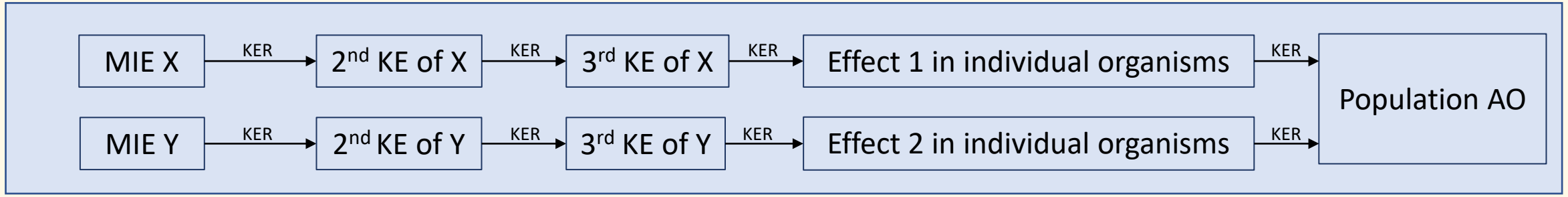


Category 3C: Interactions at a common AO

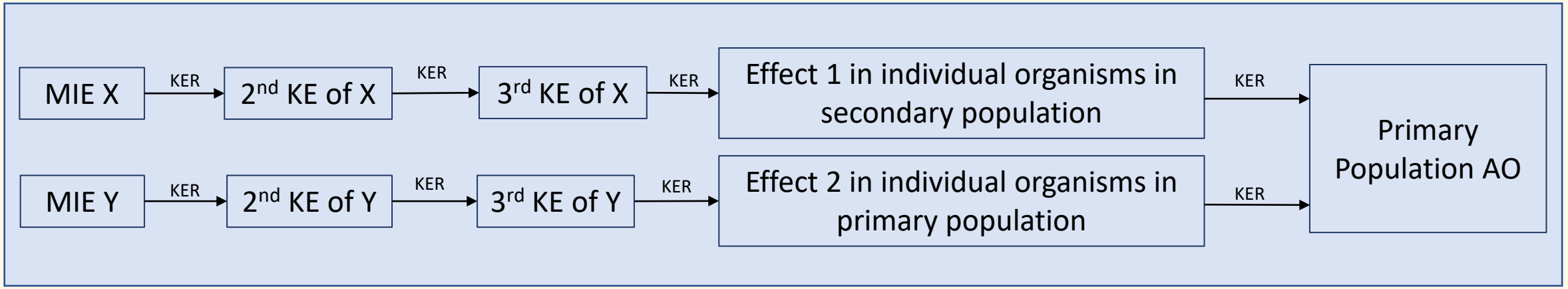


AOP – Population level

Category 4A: Population-based interactions



Category 4B: Ecosystem-based interactions

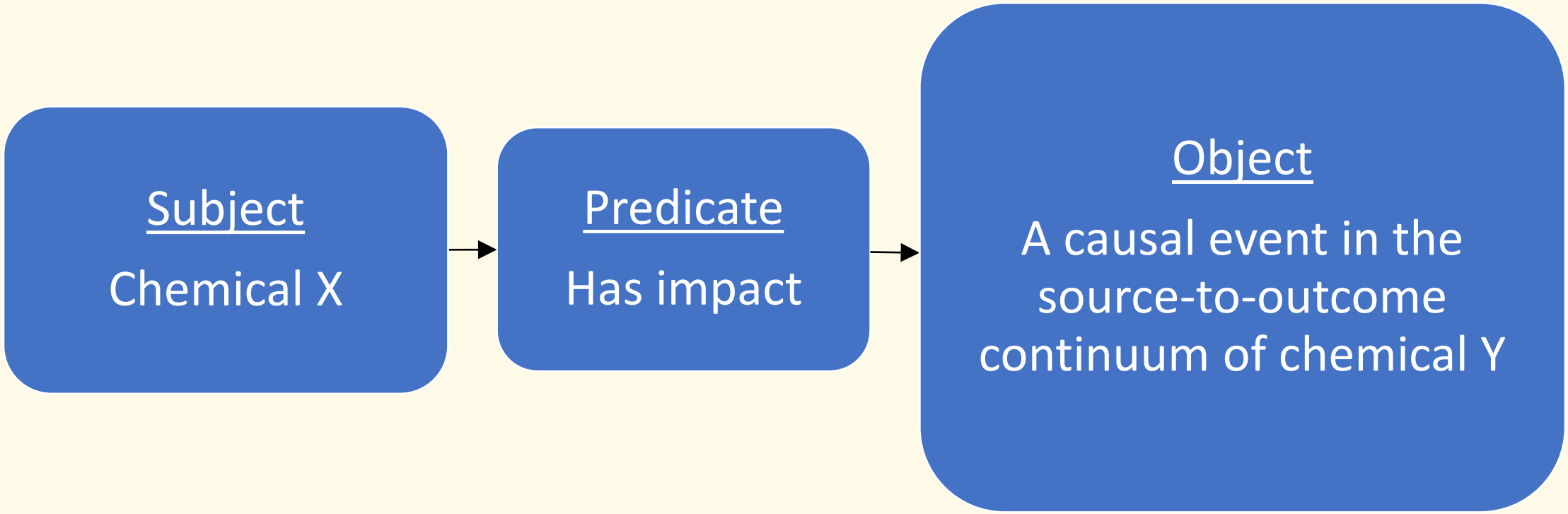


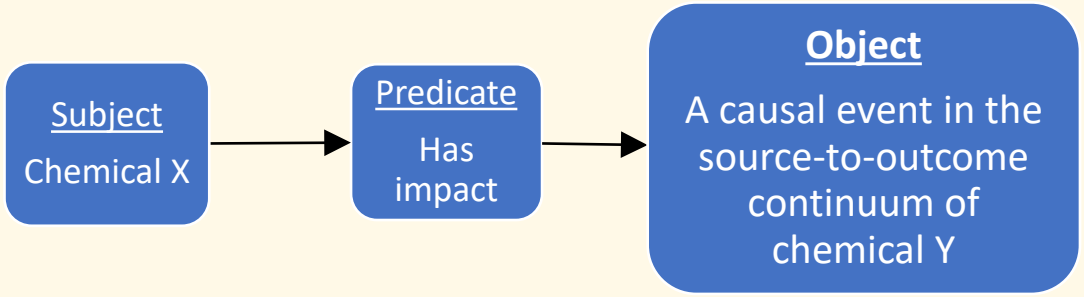
The proposed taxonomy as a straw person

- Category 1. Interactions in release, fate, transport and exposure processes of Y
  - **Category 1A. Change in the movement of Y in the environment**
  - **Category 1B. Change in the conversion of Y to Y' in the environment**
  - **Category 1C. Chemical reactions between X and Y in the environment**
- Category 2. Interactions that change the toxicokinetics of Y
  - **Category 2A. Change in the movement of Y in an organism**
  - **Category 2B. Change in the conversion of Y to Y' in an organism**
  - **Category 2C. Chemical reactions between X and Y in an organism**
- Category 3. Chemical Interactions that involve chemicals with a common AO
  - **Category 3A. Interactions involving a common MIE(s)**
  - **Category 3B. Interactions involving separate MIEs but with one or more common KEs in an AOP network**
  - **Category 3C. Interactions involving separate MIEs that converge to a common AO but have no other common KEs**
- Category 4. Interactions leading to an adverse outcome in a population-based AO
  - **Category 4A. Separate adverse effects affecting a common population**
  - **Category 4B. Chemicals that impact a population directly and indirectly by affecting another species**

The framework and informatics

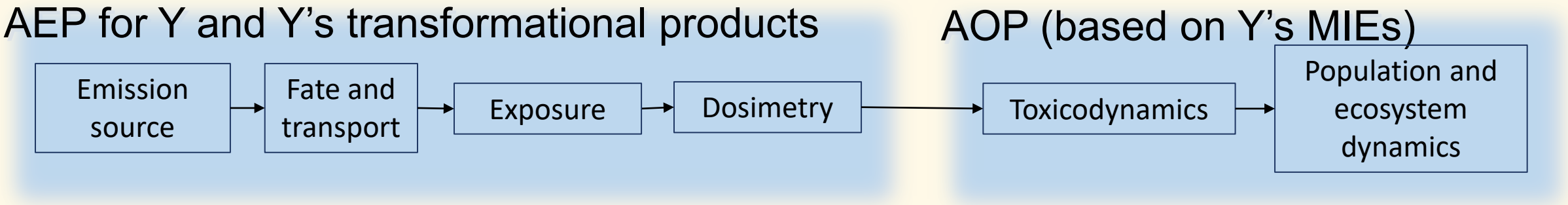
Directed interaction forms the basis for a semantic triple

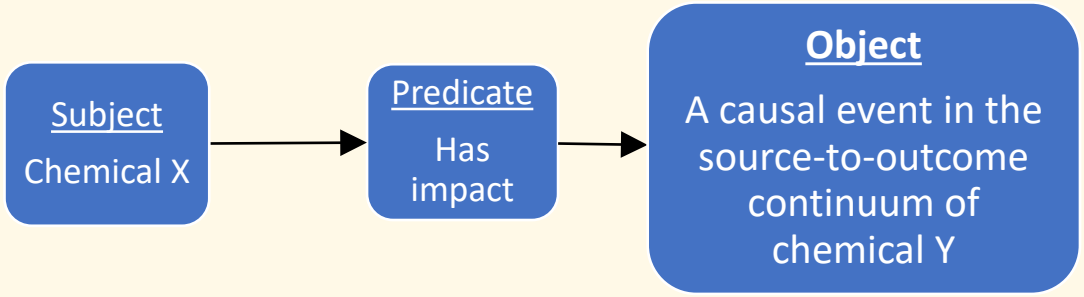




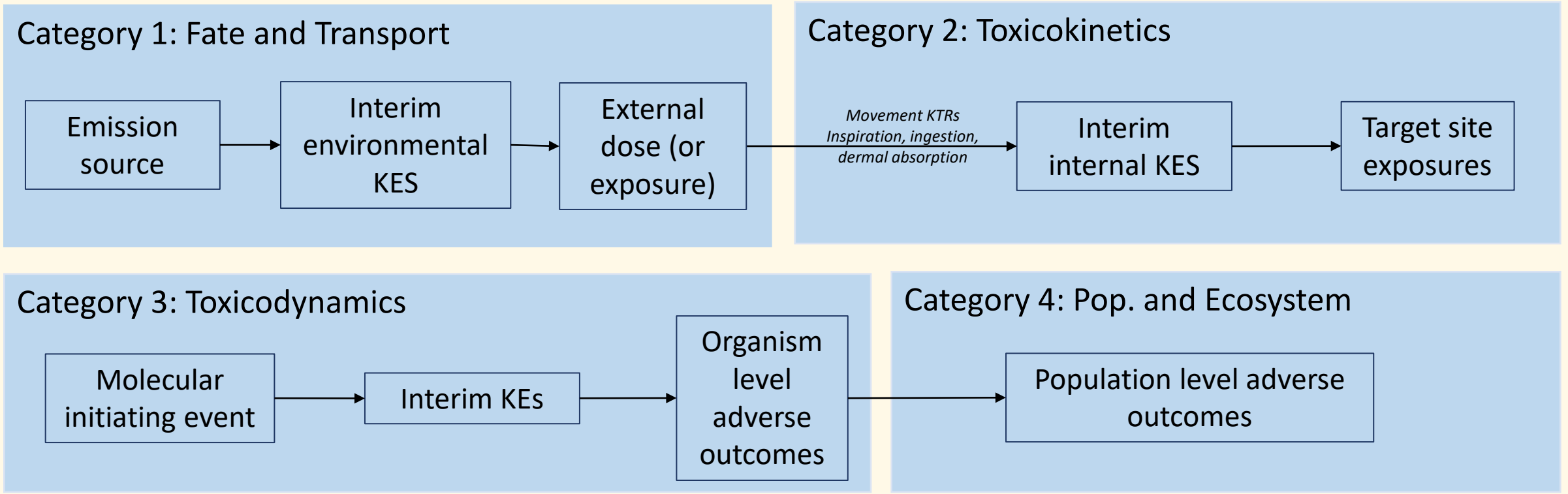
Objects: Events in source-to-outcome continuum of chemical Y

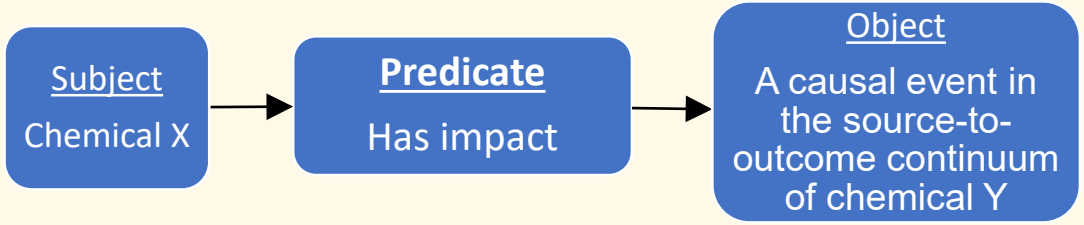
Defined in terms of Y's AEP-AOP framework





Top tier of taxonomy of interactions based on location in the continuum

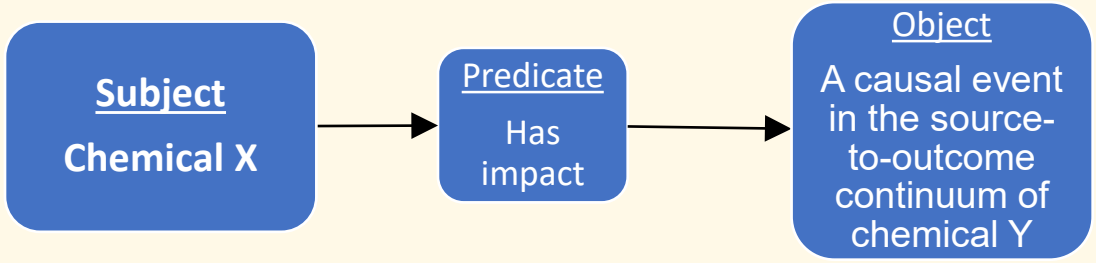




Predicate: Impact of X on the event in the source-to-outcome continuum of Y

- The nature of the impact an be diverse:
  - Increase or decrease the TSE associated with a source
  - Increase or decrease the response associated with a specific intensity and duration of an MIE by triggering MIEs for AOP that interact with Y's AOPs.
  - Create reaction products for chemical Y or Y's metabolites (XY)
  - Create new key events and AOs
- Impacts are categorized differently for events in the AEP and AOP

Subject: Chemical X



- Chemical X is defined as the “acting” agent
- Chemical X, or its effects, must share the environment/organism during the time of the release-exposure-response events of chemical Y
- The ability of chemical X to act are due to its physical, chemical, or toxicological properties
- Chemical X has its own AEP and AOP separate from chemical Y’s
- Such data are metadata for chemical X in the semantic triple

Storing data as triples

- For some pairs of chemicals data are only tracked in one direction

  The ability of X to affect and event on the source-to-outcome continuum of Y

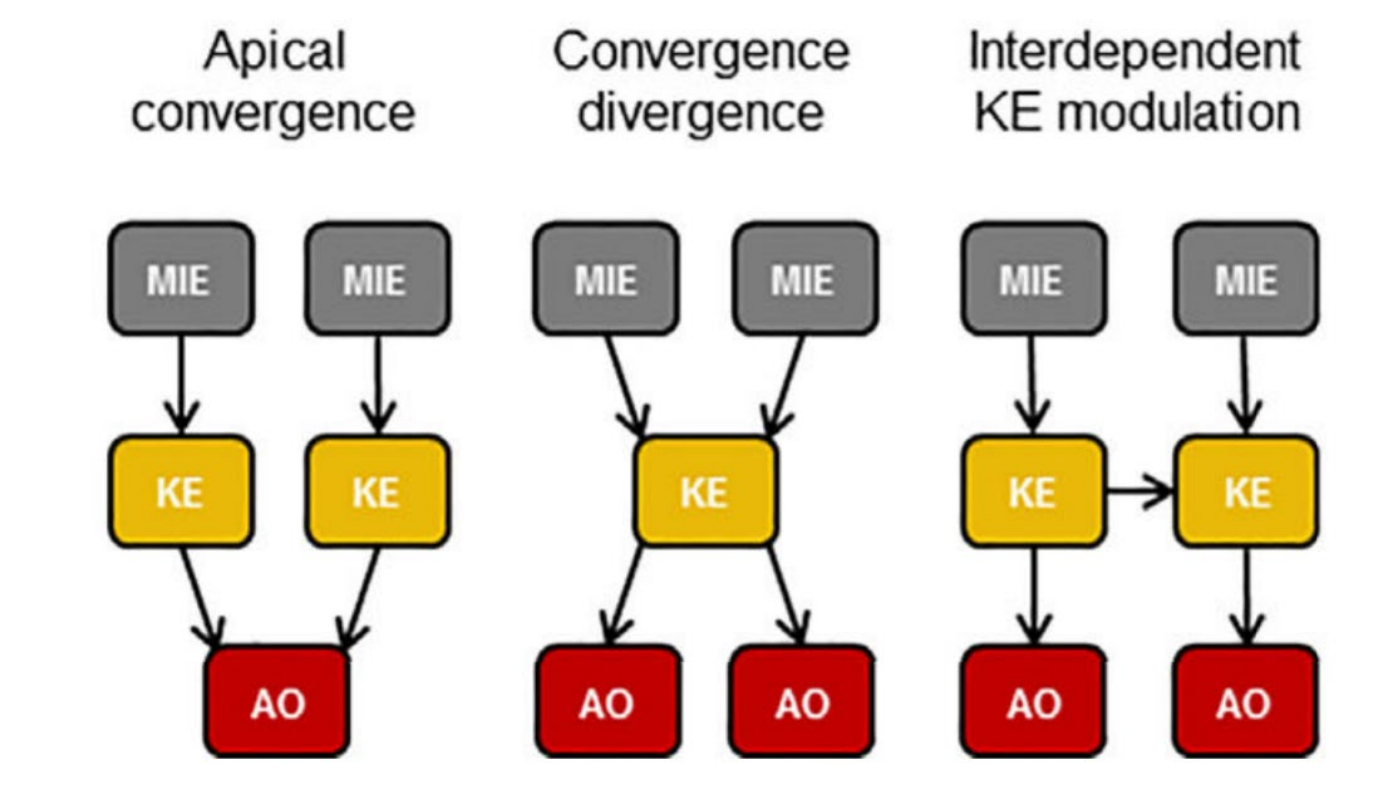
- For other pairs of chemical data are tracked in both directions

  The ability of X to affect an event on the source-to-outcome continuum of Y

  The ability of Y to affect an event on the source-to-outcome continuum of X

AEP-AOP networks

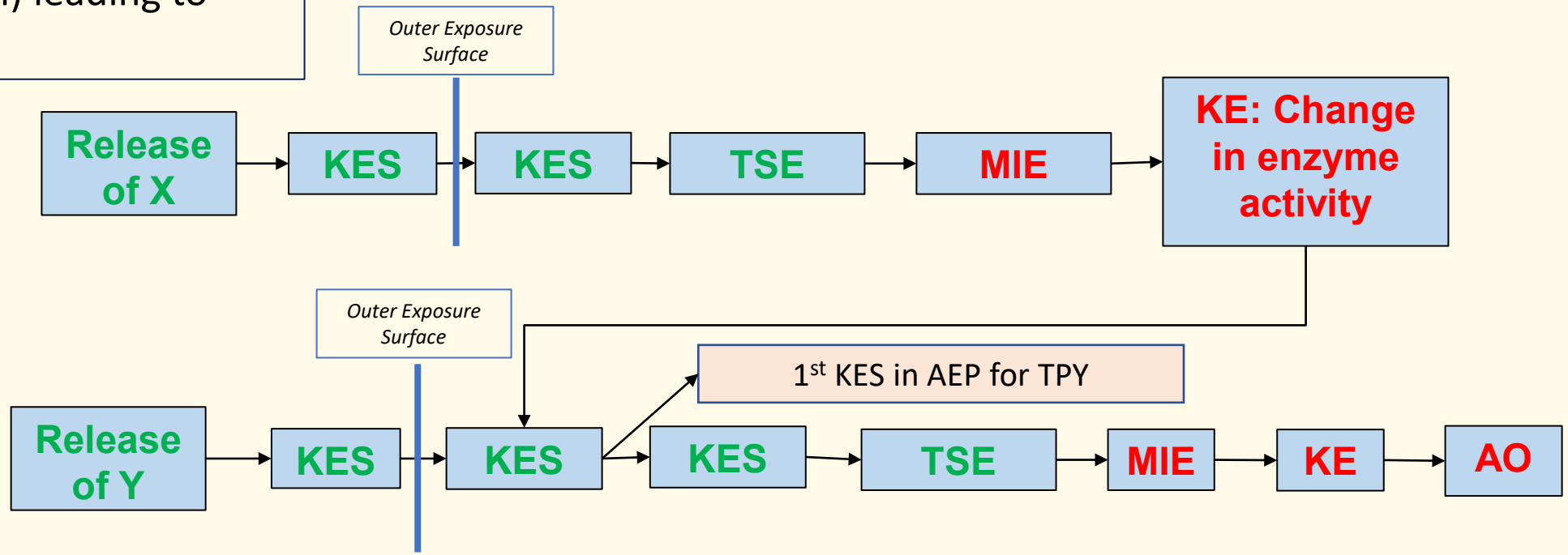
AOP networks have been proposed to address toxicodynamic interactions resulting from chemicals triggering different MIEs



Villeneuve et al. 2017

Combined AEP-AOP networks are required to describe toxicokinetic interactions

Category 2B interaction Grapefruit juice and drug metabolism:
A KE in the AOP of a chemical in grapefruit juice affects the KTR in a drugs' AEP (detoxification) leading to potentiation of the drug.



Building bridges between mixture toxicology and AOP and AEP by redefining the terms and concepts of mixture toxicology

Unlike the new definitions for interaction and non-interaction presented above, these definitions do not seek to change the existing meanings of the terms.

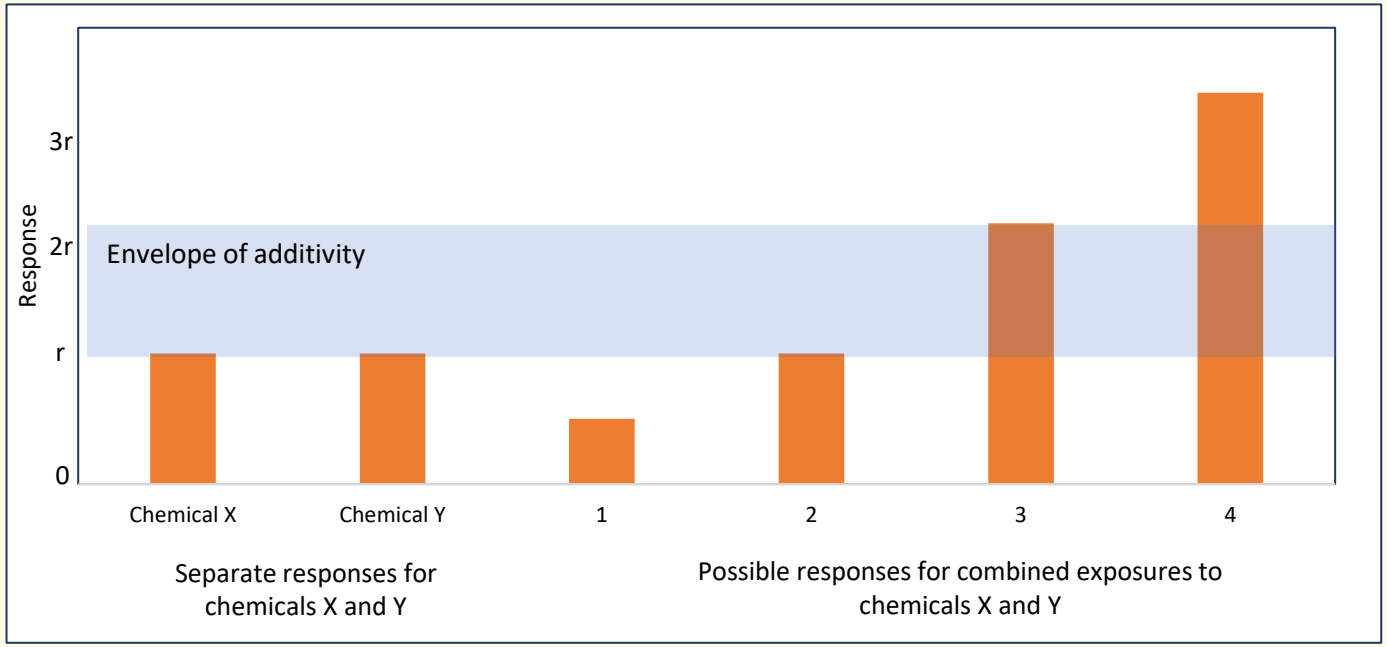
Rather they are meant to be bridges between definitions based on empirical *in vivo* toxicity data and the mechanism data generated by NAMs and organized in terms of AOPs and AEPs.

Historical approaches to assessing chemical interactions in *in vivo* models

Defined by response data for groups of chemicals measured separately and together

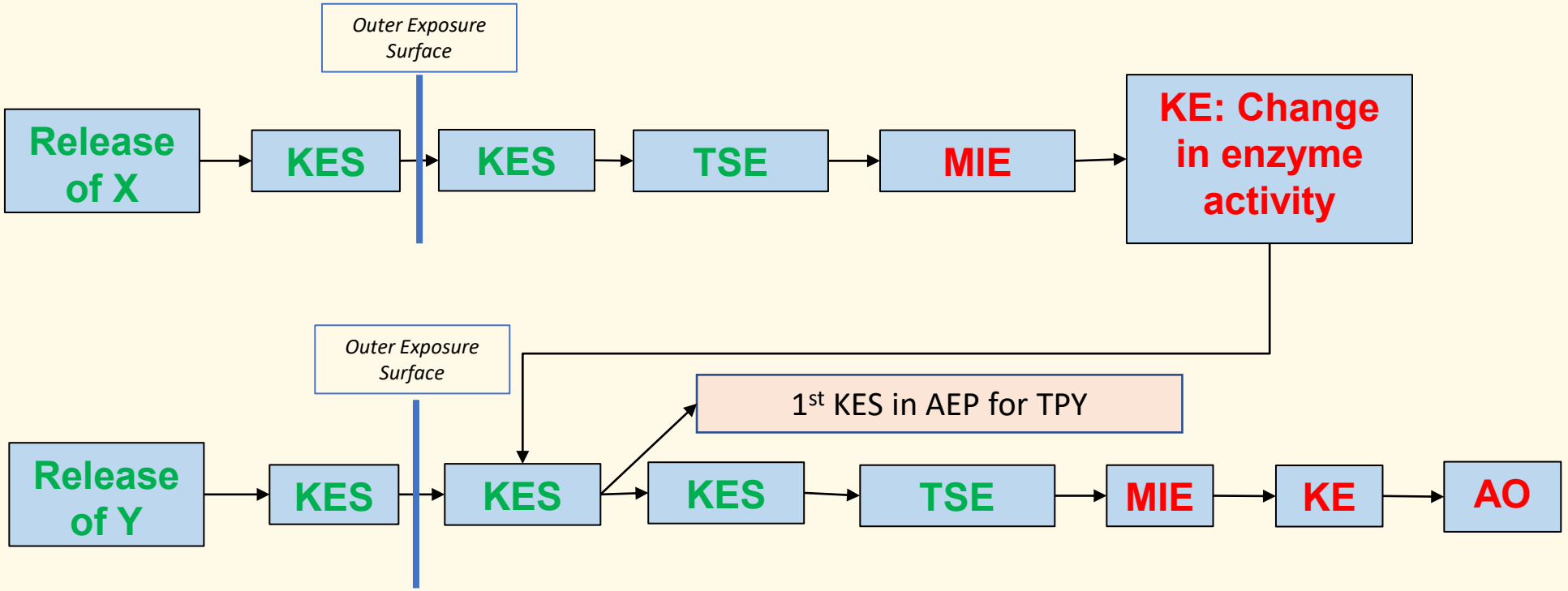
Such data provides the basis for categories of interaction:

- Dose and response additivity,
- Synergy/antagonism,
- Potentiation/inhibition, and
- Initiation and promotion



Interaction thresholds: when chemical X has a specific type of interaction with Y at one dose of X but not at a lower dose

Thresholds of interactions have been observed in empirical measurements of joint response. One of the mechanisms by which such interaction thresholds occur is when chemical X causes its impact by means of its toxicological effects



Most interactions are expected to have thresholds!

Interactions in categories 1B, 1C, 2B, 2C, 3B, 3C, 4A, and 4B will have thresholds.

Dose addition

Dose addition occurs between two chemicals (X and Y) when a prior, or concurrent, exposure to chemical X causes an increase in the intensity or duration of the MIE that occurs in response to Y by acting as if it was a concurrent toxicity weighted TSE of Y.

Dose addition has no interaction threshold.

Dose addition only occurs between chemicals when they have common MIEs (Category 3A). Having common KEs or common AOs is required but is not sufficient for demonstrating that dose addition occurs.

Response addition

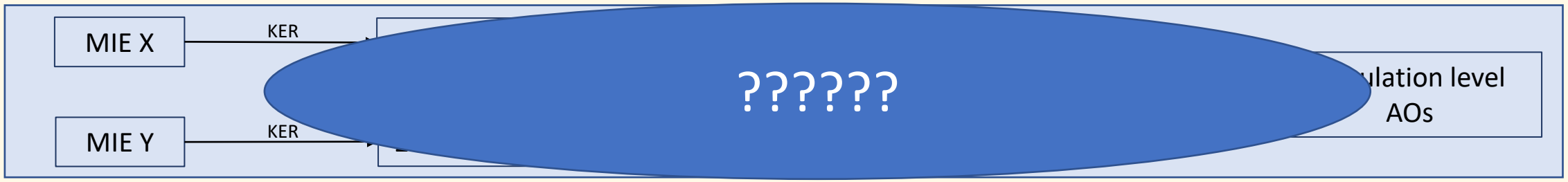
Response addition occurs between two chemicals (X and Y) when a prior, or concurrent, exposure to chemical X causes an AO in an exposed population and changes the response to a dose of Y by reducing the number of individuals where the AO has not occurred.

Response addition occurs between chemicals that do not share a common MIE or a common KE but have a common AO in an AOP network (Category 3C).

AOP – Organism level

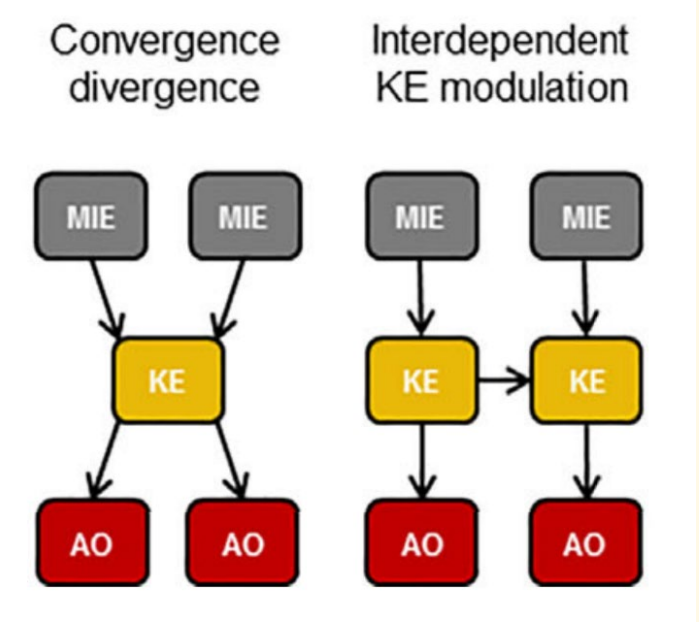
Category 3A: Interactions at a common MIE

Category 3B: Interactions at a common KE



Category 3C: Interactions at a common AO

Subcategory 3B



Villeneuve et al. 2017

- AOP networks that have one or more common KEs and no common:
  - MIEs, or
  - AOs
- Can cause a range of responses
  - Partial dose additivity
  - Antagonism
  - Synergy
  - Response additivity
- Requires construction of a qAOP network for the two chemicals
- One constant characteristic: all 3B interaction will have thresholds. The presence of X would modify to the effects of Y only when the TSE of X was sufficiently large to cause the MEI (and certain other KEs) that are prior to the KE that interacts with a KE on chemical Y's AOP.

Synergy

Synergy occurs between two chemicals, X and Y, when a prior, or concurrent, exposure to chemical X causes an increase in the response to a release of Y from a source by:

1) increasing the ratio of the amount of Y released by a source and the TSE for Y, or its active metabolite (kinetic synergy), or
2) increasing the probability that a MIE of given intensity and duration will result in the AO (dynamic synergy).

Antagonism

Antagonism occurs between two chemicals, X and Y, when a prior or concurrent exposure to chemical X causes a decrease in the response to a release of Y from a source by:

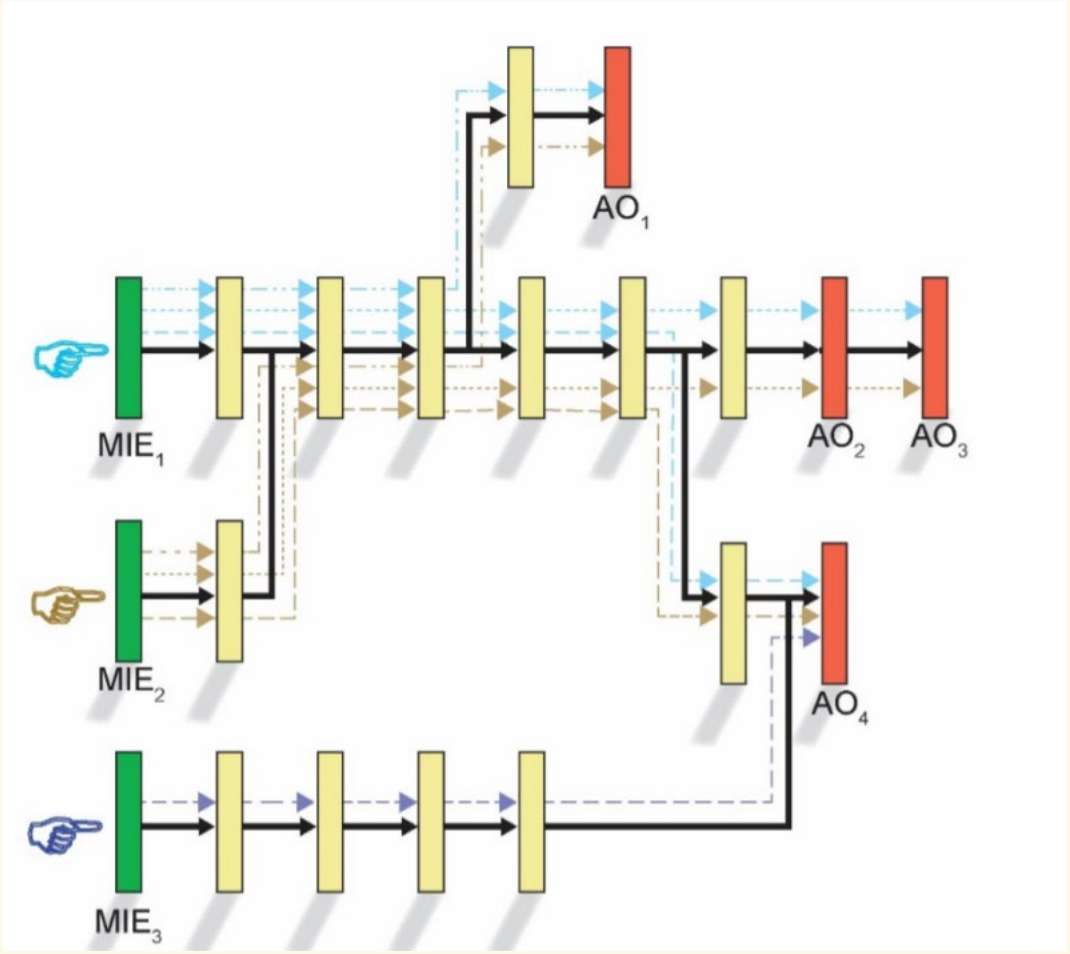
(1) decreasing the ratio of the amount of Y released by a source and the TSE for Y, or its active metabolite (kinetic antagonism), or

(2) decreasing the probability that an MIE of a given intensity and duration will result in the adverse outcome (dynamic antagonism).

Neither chemical causes an AO independently but do so together

- Categories 1C and 2C: creation of a new chemical
- Categories 2A and 2B: increases the TSE for Y or its metabolite to exceed the threshold of the MIE.
- Category 3B: Y causes one or more KEs that allow a KE of Y to trigger the AO (initiation and promotion)
- Categories 3A and 3C: cannot cause this behavior

Future steps



USEPA Research Brief 2017

Apply the taxonomy and semantic triple to actual studies

- Semantic triple
  - Subject (Chemical X)
    - Name, ability to cause the interaction (physical, chemical, or biological)
  - Predicate (interaction)
    - Description of the interaction
    - Colocation of X, or its effects, and events in source-to-outcome continuum of chemical Y
  - Object (Event in source-to-outcome continuum of chemical Y)
    - First level category of taxonomy
- Taxonomy
  - Decompose study results into findings on one or more mechanisms
  - Assign mechanisms to categories and subcategories
  - Develop additional tiers of categories
- Suggest revisions to the taxonomy and semantic triple based on the experience

Using groupings of interactions to direct research

- The ability of X to cause a change in the source-to-response continuums of other chemicals is a function of the physical, chemical, and toxicological properties of X
- This suggests that the potential to cause a specific type of interaction could be predicted based upon the chemical structure of X. Projects could be created to:
  - Identify chemicals known to affect other chemicals by a common mechanism (i.e. all chemicals that affect a common KTR, MIE, KER, or AO)
  - Development of QSARs to predict the potential to cause the interaction
  - Determination of threshold TSE for the ability to cause the interaction

Conclusions

- Advances in characterizing the risk implications of combined exposures requires an understanding of the mechanisms of chemical interactions
- Data on the mechanisms of chemical interactions need to be organized in ways that:
  - Apply to all portions of the source-to-outcome continuum
  - Facilitate the modeling of combined effects
  - Allow extrapolation to untested chemicals

The ideas presented here are offered as an initial step in this organization

Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Toxicology

A proposal for creating a taxonomy of chemical interactions using concepts from the aggregate exposure and adverse outcome pathways

Paul Price[1] and Jeremy Leonard[2]

Abstract

Currently, there is no single taxonomy for organizing data on the various types of chemical interactions that may affect risks from combined exposures. A taxonomy of chemical interactions is proposed that is based on a combination of the aggregate exposure pathways (AEPs) and adverse outcome pathways (AOPs) (AEP–AOP framework). The AEP–AOP framework organizes data on the causal events that ocur over the entire source–exposure–response continuum of a chemical's release. The proposed taxonomy uses this framework in two ways. First, four top-level categories are established based on the location in the continuum where a chemical interaction occurs. Second, each top-level category has two or more subcategories that are based on concepts taken from AEPs and AOPs. The categories and subcategories are potentially useful in developing standardized definitions for interaction terms and improving our understanding of the impacts of chemical interactions on risk to human health and the environment.

Addresses

[1] National Exposure Research Lab, ORD, U.S. Environmental Protection Agency, 109 TW Alexander Drive, RTP, NC, 27711 USA
[2] Oak Ridge Institute for Science and Education, Environmental Media Assessment Group, National Center for Environmental Assessment, U.S. Environmental Protection Agency, 109 TW Alexander Drive, RTP, NC, 27711 USA

Corresponding author: Price, Paul (price.paul@epa.gov)

Current Opinion in Toxicology 2019, 16:58–66
This review comes from a themed issue on Systems Toxicology
This review comes from a themed issue on Systems Toxicology
Available online 30 May 2019
For a complete overview see the Issue and the Editorial
https://doi.org/10.1016/j.cotox.2019.05.007
2468-2020/Published by Elsevier B.V.

Keywords
Taxonomy, Chemical interactions, Aggregate exposure pathway (AEP), Adverse outcome pathway (AOP).

1. Introduction

Currently, there is no single framework for categorizing the diverse types of chemical interactions that affect the adverse human and ecological outcomes from chemicals. While multiple individuals and organizations have proposed methods of organizing information on the effects of combined exposures to chemicals [1–7], these approaches have not considered the entire source–exposure–response continuum. In many instances, such approaches have only addressed interactions between chemicals that produce a common adverse outcome (AO) in *in vivo* models [7] or that only address toxicological interactions in individual organisms [2]. This article offers an approach that has the potent[illegible] gap.

Here, we propose a taxonomy tha[illegible] based [illegible] aggregate exposure pathway (AEP) framework [8–10] and the adverse outcome pathway (AOP) framework [11–13].[1] In this article[illegible] that the combination of AEPs and AOPs (AEP–AOP) provides a useful framework for organizing the diverse types of chemical interactions into a hierarchical system of mutually exclusive categories. These categories can provide a more detailed organization of interactions that have at best only been broadly characterized in earlier approaches. In addition, the categories organize interactions into groups with common attributes. As a result, the taxonomy can aid in the understanding and management of impacts of chemical interactions on human health and the environment.

The proposed taxonomy is presented as an initial work. The concepts in this article are offered as a discussion starter, and we welcome additional ideas, modifications, and suggestions. This article begins with a brief review of relevant components of AEPs and AOPs, followed by a description of the taxonomy and a brief discussion.

2. The combined AEP–AOP framework

The AEP–AOP framework is an objective system for organizing information on events occurring along the source–exposure–response continuum (Figure 1A), using concepts from graph theory. In an AEP, chemical exposure is defined in terms of one or

[1] AEP–AOP: aggregate exposure pathway–adverse outcome pathway; KES, key event state; KTR, key transitional relationship; KE, key event; KER, key event relationship; AO, adverse outcome.

Questions ?

Environment International 138 (2020) 105673
Contents lists available at ScienceDirect
Environment International
journal homepage: www.elsevier.com/locate/envint

Organizing mechanism-related information on chemical interactions using a framework based on the aggregate exposure and adverse outcome pathways

Paul S. Price[a,*], Annie M. Jarabek[a], Lyle D. Burgoon[b]

[a] Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, 109 TW Alexander Drive, Research Triangle Park, NC 27711, United States
[b] Environmental Laboratory, US Army Engineer Research and Development Center, Research Triangle Park, NC, United States

ARTICLE INFO

Handling editor: Adrian Covaci
Keywords:
[illegible]chemical interactions
[illegible]ixture toxicity
[illegible]iverse [illegible]thway
[illegible]gregate [illegible]posure pathway

ABSTRACT

This paper presents a framework for organizing and accessing mechanistic data on chemical interactions. The framework is designed to support the assessment of risks from combined chemical exposures. The framework covers interactions between chemicals that occur over the entire source-to-outcome continuum including interactions that are studied in the fields of chemical transport, environmental fate, exposure assessment, dosimetry, and individual and population-based adverse outcomes. The framework proposes to organize data using a semantic triple of a chemical (subject), has impact (predicate), and a causal event on the source-to-outcome continuum of a second chemical (object). The location of the causal event on the source-to-outcome continuum and the nature of the impact are used as the basis for a taxonomy of interactions. The approach also builds on concepts from the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP). The framework proposes the linking of AEPs of multiple chemicals and the AOP networks relevant to those chemicals to form AEP-AOP networks that describe chemical interactions that cannot be characterized using AOP networks alone. Such AEP-AOP networks will aid the construction of workflows for both experimental design and the systematic review or evaluation performed in risk assessments. Finally, the framework is used to link the constructs of existing component-based approaches for mixture toxicology to specific categories in the interaction taxonomy.

1. Introduction

Toxicology, exposure science, and chemical risk assessment are in the midst of a transformation. Assessors are moving towards the use of *in vitro* assays and *in silico* predictions that provide insights on the mechanisms that cause adverse outcomes (AOs) (NRC, 2007). The methodologies driving this transformation have been referred to as New Approach Methodologies or NAMs (Pham et al., 2019; Wambaugh et al., 2019). *In vivo* toxicity data are limited to a relatively small number of substances. Because of the large, and increasing, number of chemicals in commerce it is envisioned that the majority of chemicals will be evaluated in the future using NAMs rather than data from *in vivo* models of toxicity (Kavlock et al., 2018). The benefits of NAMs are perhaps more critical to the study of the effects of chemical mixtures than the effects of single chemicals (Hernandez et al., 2019). There are more combinations of chemicals than individual chemicals and dose response for combined exposures are more complex than those for individual chemicals. Following Nelms et al. (2018) and Bopp et al. (2019), the term "chemical mixtures" is defined in this paper as an organism's or population's combined exposures to two or more chemicals, where the period of time between the exposures is sufficiently small as to allow the effects of one chemical to influence the response of the organism or population to one or more other chemicals. Chemical mixtures include intentional discrete mixtures (e.g., consumer products) and unintentional discrete mixtures (e.g., industrial effluents), and concurrent exposures to chemicals from multiple sources.

The hallmark of NAMs is to illuminate the mechanisms that determine the causal events in the source – exposure – dose – outcome continuum that describes the ability of a chemical to pose risks to humans and the environment (Cohen-Hubal et al., 2010; Hines et al.,

Abbreviations: ADME, absorption, distribution, metabolism and elimination; AEP, Aggregate Exposure Pathway; AO, Adverse Outcome; AOP, Adverse Outcome Pathway; CSM, Conceptual Site Model; ICKE, Initial Common Key Event; KE, Key Event; KER, Key Event Relationship; KES, Key Exposure State; KTR, Key Transition Rate; MIE, Molecular Initiating Event; NAM, New Approach Methodology; RDF, Resource Description Framework; TSE, Target Site Exposure; qAOP, quantitative Adverse Outcome Pathway

* Corresponding author.
E-mail address: paul.price@pipeline.com (P.S. Price).

https://doi.org/10.1016/j.envint.2020.105673
Received 12 December 2019; Received in revised form 16 March 2020; Accepted 17 March 2020
Available online 24 March 2020