Exploring Current Read-across Applications and Needs Among U.S. Federal Agencies

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Introduction

- To raise awareness and facilitate harmonization of the publicly available read-across tools across U.S. agencies, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) established a Read-across Workgroup (RAWG). This is one of several ad hoc groups ICCVAM has convened to implement the ICCVAM Strategic Roadmap (ICCVAM 2018).
- The RAWG includes representatives of U.S. federal agencies and partner organizations in the International Cooperation on Alternative Test Methods (**Table 1**).
- This poster summarizes information gathered by the RAWG of available tools, relevant applications, decision contexts, and needs relevant to read-across applications for U.S. federal agencies.

Table 1. RAWG Members

U.S. Agencies	Agency for Toxic Substances and Disease Registry (ATSDR)
	U.S. Consumer Product Safety Commission (CPSC)
	U.S. Department of Defense (DoD)
	U.S. Environmental Protection Agency (EPA)
	U.S. Food and Drug Administration (FDA)
	National Institute of Environmental Health Sciences (NIEHS)
	National Library of Medicine (NLM)
ICATM Partners	European Union Reference Laboratory for Alternatives to Animal Testing (EURL-ECVAM)
	Japanese Center for the Validation of Alternative Methods (JaCVAM)

RAWG Charge

- Catalog ongoing read-across experiences and needs across different agencies and highlight the different decision contexts of interest
- Identify existing read-across resources, including existing technical guidance and software tools, that will highlight the applicability of read-across tools to ensure appropriate context of use
- Identify high-quality data sources to evaluate read-across analyses for regulatory applications
- Identify case studies that demonstrate utility of read-across analyses in a regulatory setting
- Determine key data needs for regulatory acceptance of read-across approaches
- Summarize best practices for the application and implementation of read-across within regulatory settings
- Establish new collaborations to address research needs to assure scientific confidence in read-across
- Work with international partners to ensure international harmonization on use and application of read-across approaches

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The views expressed above do not necessarily represent the official positions of any federal agency.

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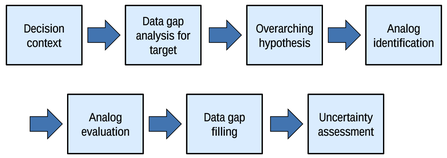
Read-across Workflow

- Read-across is a method of filling a data gap that uses known information on the property of a substance (source chemical) to make a prediction of the same property for a similar substance (target chemical).
- The seven key steps in a typical read-across workflow are shown below.



Decision Context

- Define the decision context to clarify the scope and purpose of the problem being considered and ensure fit-for-purpose application of read-across.
- The decision context might relate to a hazard-level screening assessment, a risk assessment, or a prioritization scheme.

Data Gap Analysis

- Assess what data gaps exist for the target substance of interest and for which endpoints.
- This could indicate whether other data gap-filling techniques, such as quantitative structure-activity relationship analyses or *in vitro* testing, might be more applicable.

Overarching Hypothesis

- Evaluate what is known about the target substance to guide identification of source analogs.
- Factors to consider include common functional groups or the target substance's likely mechanism of action.

Analog Identification

- The search for candidate source analogs may be tailored to the endpoint under study or may be a search based solely on structural similarity.

Analog Evaluation

- Evaluate the relevance and availability of toxicity information for the candidate source analogs based on general and endpoint-specific considerations.

Data Gap Filling

- Use either an expert-driven or algorithmically derived process to make the read-across prediction.

Uncertainty Assessment:

- Assess the performance and characterize the confidence associated with the prediction.
- Consider whether the level of uncertainty is acceptable for the decision context and if not, what additional information might be needed.

Publicly Available Read-across Tools and Results of the RAWG Survey

- **Table 2** lists characteristics of eight publicly available read-across tools identified by the RAWG as potentially useful to federal agencies for research or regulatory applications.
- RAWG findings on the use of these tools by seven offices spanning four federal agencies and relevant guidance are summarized in **Table 3**. Our aim was to identify the guidance, resources, and frameworks currently in use and understand what needs remain in these areas.
- **Table 4** provides a snapshot of the decision contexts and needs for read-across within the surveyed U.S. agencies. The decision contexts are varied in scope and emphasize the uncertainty that can be tolerated and the resources that will be most useful to each agency.
- **Table 5** summarizes two case studies developed by the RAWG that demonstrate utility of read-across analyses in a regulatory setting and identify key data needs for regulatory acceptance.

Table 2. Publicly Available Read-across Tools

	Type of Tool	Available from	Accepted Chemical Input	Endpoint Coverage	Analog Identification Approach	Neighbor Selection	Data Source	Steps Covered
AIM	Standalone	https://www.epa.gov/tsca-screening-tools/analog-identification-methodology-aim-tool	CAS, name, SMILES, structure drawing/import	N/A	Fragment matching	Automatic	Tool provides inventory index	Analog identification
Toxmatch	Standalone	https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/qsar_tools/toxmatch	CAS, name, SMILES, InChI	Any; based on user input	Distance and correlation-based similarity indices based on descriptors or fingerprints	Automatic	User or tool provided	All except uncertainty assessment
Ambit	Web-based and standalone	http://cefic-lri.org/lri_toolbox/ambit/	Name, SMILES, InChI	IUCLID 5-supported endpoints (43 total)	Substructure or similarity searching using structure, name, SMILES, InChI	Manual	User or tool provided	All except uncertainty assessment
OECD QSAR Toolbox	Standalone and client/server	https://qsartoolbox.org/	CAS, name, SMILES, structure drawing, structure data file (sdf)	Any, per available regulatory endpoints	Category definition followed by subcategorizations	Automatic + manual filter	User or tool provided	All
CBRA	Standalone	http://www.fourches-laboratory.com/software	Mol file, descriptors as txt	Any; based on user input	Tanimoto distance using chemical and biological descriptors	Automatic	User provided	All except uncertainty assessment
ToxRead	Standalone	http://www.toxread.eu/	SMILES	Mutagenicity and bioconcentration factor	VEGA similarity algorithm	Automatic	Tool provided (EU ANTARES project)	All except uncertainty assessment
CIIPro	Web-based	http://ciipro.rtugets.edu/	PubChem CID, CAS, IUPAC, SMILES, InChI	Any; based on user input	Weighted estimated biological similarity	Automatic + manual filter	User provided; tool provides PubChem *in vitro* data	All except uncertainty assessment
GenRA	Web-based via the EPA CompTox Chemicals Dashboard	https://comptox.epa.gov/dashboard	Linked to the DSSTox inventory	Repeat-dose toxicity endpoints covered in the ToxRefDB v 1.0	Jaccard similarity index based on different chemical fingerprints: Morgan, Torsion, Chemotype	Automatic + manual filter	Tool provided (ToxRef DB)	All

Table 3. Agency-specific Guidance and Other Resources

Agency	Guidance, Policy, or Other Document	Resources	Framework/ Approaches
ATSDR	None	• OECD QSAR Toolbox • ToxRead • SimulationsPlus • TOPKAT • CaseTox • Leadscope	• OECD Grouping Guidance • Read-across Framework
DOD	None	• New read-across tool in development (Army) • OECD QSAR Toolbox (Navy/Air Force)	None
EPA OPPT	• Frank R. Lautenberg Chemical Safety for the 21st Century Act (EPA 2017) • EPA Strategic Plan • TSCA New Chemicals Program Chemical Categories (EPA 2010)	• AIM • ChemACE • Oncologic • OECD QSAR Toolbox	• OECD Grouping Guidance
EPA NCCT	None	• GenRA	Not Applicable
EPA NCEA	None	• ChemIDplus database • DSSTox database • ChemACE • OECD QSAR Toolbox	• Expert driven read-across framework (Wang et al. 2012)
NIH NLM	None	• PubMed • Hazardous Substances Data Bank • International Estimates for Risk database • ChemIDplus • ToxTutor	• Provide access to training, publications and databases useful for read-across information

NCCT = National Center for Computational Toxicology; NCEA = National Center for Environmental Assessment; NIH = National Institutes of Health; OECD = Organisation for Economic Co-operation and Development; OPPT = Office of Pollution Prevention and Toxics.

Table 4. Agency-specific Decision Contexts and Needs for Read-across

Agency	Decision Context	Agency Needs to Apply Read-across
ATSDR	• Supporting emergency response • Filling data gaps for chemicals of interest • Hazard assessments of chemicals found at waste sites	• Guidance for the use of read-across for emergency response and for chemicals found at waste sites • Read-across application to chemical mixtures • Identifying best practices for the use of read-across for specific contexts
CPSC	• Risk assessment of chemicals in consumer products	• Training and guidance on application of read-across • Identifying best practices for the use of read-across for specific contexts
DoD	• Screening for occupational safety • Screening for environmental safety • Information for emergency response, product registration and exposure limits for use by internal clients	• Use criteria • Training and guidance on application of read-across • Identifying best practices for the use of read-across for specific contexts
EPA NCEA	• Support Superfund-related activities in site-specific screening and prioritization and quantitative risk assessment of data-poor chemicals at contaminated sites	• Integration of software tools and new approach methodologies data to augment expert judgment and increase confidence in read-across assessments • Guidance on systematic weight-of-evidence approaches to evaluate similarity and uncertainty
EPA OPPT	• Prioritization of existing chemicals • Risk evaluation of new and existing chemicals	• Refinement to the New Chemicals Categories • List of acceptable new approach methodologies
FDA CDRH	• Risk assessment of medical devices	• Guidance for the use of read-across for toxicological risk assessment of medical devices • Qualify read-across to support device evaluation and regulatory decision making in the Medical Device Development Tools program (FDA 2017)
FDA CFSAN	• Hazard identification and prioritization	• Guidance for the use of read-across for contaminants, dietary ingredients within dietary supplements, food contact substances, and cosmetic ingredients
ICCVAM	• Support U.S. agency needs and decision contexts	• Validation of read-across approaches

CDRH = Center for Devices and Radiological Health; CFSAN = Center for Food Safety and Applied Nutrition; NCEA = National Center for Environmental Assessment; OPPT = Office of Pollution Prevention and Toxics; PPRTV = Provisional Peer Reviewed Toxicity Values.

Table 5. Case Studies from Two Federal Agencies

Read-across Workflow	Case Study 1: EPA NCEA	Case Study 2: FDA CDRH
Decision context	Derivation of an inhalation RfC for n-heptanal for a screening level Superfund Health Risk value	Risk assessment of Substance X in a medical device; derivation of a POD for a margin of safety calculation
Data gap analysis for target	Absence of repeat-dose toxicity data for inhalation to derive a POD and a screening level RfC value	Repeat-dose toxicity information needed to derive a POD
Overarching hypothesis	Identify chemicals that are structurally, metabolically, or toxicologically similar to n-heptanal	No overarching hypothesis was provided by the registrant.
Analog identification	Three potential analogs were identified with 33-69% structural similarity and available inhalation RfC values. The target chemical and identified analogs shared a reactive moiety associated with the expected toxicity (i.e. nasal lesions).	Substance X was identified as a discrete substance. Analogs were identified with 10-20% structural similarity. Metabolites were profiled and used to read-across to the target chemical.
Analog evaluation	Two of the analogs identified were deemed suitable on the basis of structural, metabolic, and toxicologic comparisons with respect to the target chemical.	One predicted metabolite had available repeat-dose toxicity data.
Data gap filling	From the two remaining suitable analogs, the closest structural analog was selected as a source chemical and its associated POD was read-across to n-heptanal.	The predicted metabolite was used as a source chemical to derive a POD for a margin of safety calculation for Substance X.
Uncertainty assessment	Uncertainty factors were described and applied to POD to derive the screening level RfC value.	No uncertainty assessment was provided by the registrant.

CDRH = Center for Devices and Radiological Health; NCEA = National Center for Environmental Assessment; POD = point of departure; RfC = reference concentration.

Conclusions

- Among the federal agencies surveyed, read-across is most broadly used at EPA.
- The needs and decision contexts vary substantially across federal agencies.
- Several agencies are interested in read-across for mixtures, but there is currently minimal guidance available for this particular application.
- An overarching question that remains is how to adequately and reproducibly characterize the scientific confidence of a read-across prediction.
- There is a need for agencies to characterize their chemical landscapes to facilitate evaluation of the applicability of the existing read-across tools described.

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