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Read-across for toxicological data gap filling: state-of-the-art, challenges and future needs

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Read-across is a well-established New Approach Methodology (NAM). Its approach and methods are mature and widely used, especially for data-gap filling relating to *in vivo* tests. It is supported by guidance and reporting templates, as well as computational tools. However, greater expertise and clarity are required to gain further acceptance. Challenges and needs focus on improving the acceptability of read-across predictions. These include: 1) understanding how uncertainties are quantified and how the overall (tolerable) uncertainty can be defined, 2) assessing similarity between target and source molecules, especially beyond strict 2D structural similarity, whilst avoiding activity cliffs, 3) key similarity challenges exist in metabolism, including the ability to confirm the principle pathways and biotransformations leading to toxicologically significant metabolites, as well as the rates of their formation, 4) the lack of suitable data to support read-across; thus, efforts to justify using non-standard data should continue to be developed, and 5) the use of artificial intelligence (AI) in read-across presenting its own set of challenges, which are, however, outweighed by the opportunities and gains. The role of AI in assessing similarity and, indeed, all aspects of read-across will grow, but at this time, how and at what speed it will grow is unknown. Read-across also has the potential to assist in the integration of non-animal chemical safety assessments and Next Generation Risk Assessment (NGRA).

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Introduction

Read-across is a well-established *in silico* (computational) New Approach Methodology (NAM) frequently used to address toxicological and other data gaps, especially for industrial chemicals [1,2]. It is based on the premise that similar substances will have similar properties and effects; hence, information from a data-rich substance can inform a similar data-poor substance [3]. Similarity between substances may be defined in a number of ways, including computed similarity metrics, common functional groups (often relating to a similar mechanism of action or metabolism), and being a member of a common chemical class, among others [4,5].

The aim of this 'Comment' was to provide the authors' personal insights into where we are with read-across, their opinions on current challenges and needs, and opportunities for the future development of this approach. The views stated in this 'Comment' are those of the authors alone.

State-of-the-art of read-across

Currently, read-across can be considered a NAM in its own right and is often used as a standalone approach. It can also be applied within a tiered-testing strategy, such as an Integrated Approaches to Testing and Assessment (IATA), or as part of the implementation of Next Generation Risk Assessment (NGRA), for instance, as part of a broader read-across scheme incorporating exposure [6] or the Alternative Safety Profiling Algorithm (ASPA) [7].

Regarding the current regulatory use of read-across, there is now extensive guidance, most recently from the European Food Safety Authority (EFSA) [4] and the Organisation for Economic Cooperation and Development (OECD) [5]. These guidance documents present workflows to guide and support the implementation of read-across in a relatively standardised manner. Other documentation is available for evaluating read-across in a regulatory context, such as the European Chemicals Agency's (ECHA's) Read-Across Assessment Framework (RAAF) [8]. Despite the widespread use of read-across to fill data gaps [9], evaluations of submitted read-across predictions have identified that a significant proportion of submissions have not been accepted [10–12]. At the current time, there remains a clear need to improve

documentation and justification of similarities between target and source substances, enhance access to high-quality data, and better assess uncertainties. Several practical tools to support the implementation of read-across workflows are available, some free of charge. The most widely used computational tool for read-across is the OECD QSAR Toolbox [13,14]. In addition to these tools, templates for reporting read-across, documenting the underlying data and evaluating uncertainties have been provided, most recently by EFSA [4].

Thus, to summarise the current state of read-across use, it is widely used with high expectations, especially for replacing *in vivo* tests. Multiple uses of read-across are envisioned, from hazard identification, e.g., to support classification, prioritisation for testing, through to potency determination to support risk assessment, among other uses. It is well supported by guidance and reporting templates, as well as computational tools that facilitate the process. However, greater expertise and clarity are needed to gain acceptance of read-across for data-gap filling. The challenges and needs for read-across, therefore, centre on improving acceptability and broadening its scope and applicability.

Challenges and needs for read-across

Quantifying uncertainties and defining tolerable uncertainty

Addressing the need to improve the acceptability of read-across requires clear statements of what is acceptable for a particular purpose. One approach is to frame acceptability in terms of tolerable uncertainty, as stated by EFSA [4]. This requires clear problem formulation in read-across that specifies tolerable uncertainty for the purpose, endpoint, and substance. It is acknowledged that different purposes may require more stringent tolerable uncertainty levels; for instance, waiving the requirement for an *in vivo* animal test may necessitate intrinsically lower uncertainty in read-across than in hazard identification for classification, where classification may be itself be based on potency (e.g., acute toxicity) or evidence (e.g., endocrine disruption) and thus have differing levels of tolerable uncertainty. There is a clear need for a greater understanding of how uncertainties in read-across are quantified, how the overall uncertainty can be defined, and what its expectation is. This also requires a greater appreciation that not all elements of uncertainty have a high impact on overall uncertainty [15]. Thus, there is a need for a more global appreciation of the levels of tolerable high-impact uncertainty, which could be achieved through retrospective analysis of accepted read-across analyses. Two elements of read-across can be considered to have a high impact on overall uncertainty, regardless of the endpoint or context: the hypothesis and justification for similarity between the target and source substances, and data quality. The focus of overall uncertainty assessment should be based on these key, high-impact uncertainties. The EFSA [4] guidance demonstrates that the read-across community has learnt extensively from risk -assessment knowledge o uncertainty. Other opportunities could also be investigated, with a possible focus on improving the understanding of the credibility of computational models [16].

Assessing similarity of target and source substances and avoiding activity cliffs

A key aspect of uncertainty in read-across is the similarity between target and source molecules. As similarity drives read-across, it will always have a high impact; however, it is often acknowledged that chemical similarity alone may be insufficient to support read-across [17]. In addition, a greater appreciation of the relevant type of similarity (e.g., based on properties, toxicodynamics, toxicokinetics, metabolism, etc.) for a particular endpoint and context is required. It is known that there are different ways to describe chemical similarity (of small molecules), ranging from easy-to-compute similarity metrics to structural fragments and groupings. Metrics, or indices, of chemical similarity have been shown to be inadequate for many aspects of similarity determination [18]. Such metrics are not mechanistically based and, as such, are prone to missing 'activity cliffs', where a small change in structure can lead to considerable variation in activity [19]. Other, more bespoke methods of determining chemical similarity include the development of chemistry-based groupings, termed structure—activity groups (SAGs), based on indicator phrases (IPs) [20]. These IPs group similar molecules based on rational decisions about chemical structure that are directly attributable to adverse effects and/or mechanisms of action.

Activity cliffs in read-across pose a particular challenge, and there is a need to raise awareness and develop solutions to ensure that similarity is appropriately captured to avoid them. An activity cliff implies a change in effect, most likely due to a change in mechanism or metabolic profile. If such a change is not captured by chemical similarity, biological or mechanistic information must be included in the assessment of similarity [21]. There is also a need to identify which endpoints exhibit the most prominent activity cliffs. This is likely to be the case for complex chronic effects, notably at the organ level, and may affect developmental toxicology. There is no silver bullet for the concern over activity cliffs, and there is limited knowledge of the scale of the problem. The development of improved grouping methods, such as the aforementioned SAGs, may facilitate this.

Linked to improving similarity assessment and reducing uncertainty is the need to, where possible, systematically include additional NAM data [22]. As noted above [17], a significant challenge is that chemical similarity is

often considered to be insufficient to support or justify read-across. This is explicitly stated in the EFSA read-across workflow [4] and elsewhere [23]. Greater experience with NAM data and uncertainty assists with identifying the presence or absence of a specific mechanism and whether a lack of mechanistic knowledge is critical to supporting read-across (as confirmed by Daston et al. [21]), particularly to avoid delays caused by excessive and unnecessary data estimation or measurement. Various NAMs, including connectivity mapping (Cmap) [24], cell painting [25] and toxicogenomic data [26] have been used to support read-across hypotheses. *In vitro* NAMs may have particular functionality as a standalone similarity metric or fingerprint, to assist with similarity justifications for mixtures or unknown or variable composition, complex reaction products, or biological materials (UVCB) substances.

Defining similarity of common metabolites and/or degradants

One of the read-across similarity scenarios is the production of the same, or highly similar, seminal metabolite or degradant. Whilst this approach is likely to be more widely applied in the future, we are currently limited by our knowledge and technology in supporting and justifying such a hypothesis. These challenges include the inability to confirm the identity of the principal pathways and biotransformations that lead to toxicologically significant metabolites, as well as the rates at which they form. Current *in silico* methods are limited in this regard [27] although new techniques are being developed [28,29]. There may also be a requirement for experimental measurement of metabolism or degradation, such as could be provided by NAMs, to provide an acceptable read-across argument [30].

Need for high quality and relevant data for source molecules

There is a substantial need for high-quality data for the source analogue in addition to supporting NAM data for the justification of similarity. The lack of suitable data to support read-across will continue to be a major limiting factor for the approach and may restrict the applicability of read-across to well-characterised areas of chemistry, such as high-production volume (HPV) chemicals. The fundamentals of data availability are well established in the relevant guidance [6,7]; the data to be read across must be for the endpoint in question, ideally from an OECD Test Guideline study, and must have been generated under Good Laboratory Practice (GLP), with a number of schemes such as Klimisch [31] and the ToxRTool [32] being utilised to assess data quality. Since the availability of appropriate *in vivo* data will remain a limiting factor, read-across efforts to justify the use of non-standard data (e.g., from non-OECD test guideline assessments, non-validated NAM assays and mechanistic information etc.) will continue to be developed, in addition to the use of technologies such as federated learning to potentially tap into confidential, or commercially sensitive, data sources [33]. Whilst non-standard data will be encouraged, effort will be required to ensure the relevance and appropriate quality of the data.

There is a fundamental role for read-across in tiered testing strategies and NGRA in particular [6,7,34]. This is typically at one of the first tiers of NGRA, and is usually seen as being sufficient for a decision on risk assessment to be made. Whilst the acceptability of read-across is being better defined, the decision points in NGRA need to be clearly stated, such that an appropriate decision may be made. NGRA may also allow for different evidence and acceptability, for instance based on *in vitro* and *in chemico* NAMs. Another possibility may be for low-exposure compounds, where higher uncertainty may be tolerable. It is further hypothesised that the application of read-across in NGRA will foster intelligent testing using NAMs and support the use of artificial intelligence (AI), particularly machine learning (ML), to develop the next generation of *in silico* tools.

Defining the role of AI in read-across

AI is currently a hot topic across all areas of society, with its presence being increasingly felt in chemical risk assessment [35]. Regarding its use in toxicology, we are clearly at the start of AI adoption, with several potential applications [36]. There is an improving understanding of the role of AI in toxicology as being 'predictive', e.g. the use of ML in QSAR and related approaches, and 'generative', e.g., the use of large language models (LLMs) to create and assimilate text [37]. Recent, exciting, examples of the use of agentic AI have demonstrated the capability to assist in the read-across process and the utilisation of tools such as the OECD QSAR Toolbox [38]. Beyond the speed of change in this area, there are multiple challenges to the use of AI in toxicology and read-across, but these are outweighed by the opportunities and gains. However, we suggest caution. First, avoid the hype and be realistic about what is required and what can be achieved; this will require a global consideration of the issue and a two-way dialogue between AI developers and the toxicology community. Second, particularly for read-across, provide AI that is cognisant of toxicology and chemistry, i.e., has the documented knowledge of a trained expert, rather than merely access to the information. Third, provide sustainable platforms; our current technologies that are readily available, such as the OECD QSAR Toolbox, have largely been funded by government agencies. Whilst such software is 'free-to-use', it does require considerable funding and commitment to develop and

maintain. Plans and funding for large-scale informatics AI infrastructure will need further funding and/or an appropriate business model and plan.

Continual development and sustainability of read-across

As noted above, the essential practical need for the successful application of read-across is to ensure the continual update and development of computational tools and data resources. The success and uptake of the OECD QSAR Toolbox demonstrate the importance of sustainability in computational tools, and the funding and contributions that underpin the Toolbox are acknowledged and will need to be maintained [14]. Updates to the Toolbox and similar tools will be vital to enable opportunities in software infrastructure and informatics development, new databases and profilers, and changes and requirements in chemical regulation. Related to sustainability is the ongoing process of training and capacity building to ensure that appropriate standards are met for the future acceptance of read-across.

Summary: the future for read-across

The approach and methodology for toxicological read-across are well established. Whilst the general approach has changed little over three decades, we have much greater knowledge and experience in applying read-across and incorporating new types of information. This knowledge and these needs will be further developed to support the overwhelming requirement for greater acceptability of read-across predictions. Preferably, there will be an increase in the depth and complexity of similarity methods that account for knowledge of chemical space (i.e., well-investigated regions, with a low probability of activity cliffs), endpoints, and mechanisms of action, with a targeted approach to incorporating biological and computational NAMs. Associated with improvements in similarity and grouping will be better assessments of uncertainty and credibility, thereby improving acceptability. The role of AI in assessing similarity and, indeed, all aspects of read-across will grow, but at this time, how and at what speed it will grow is unknown. The identification and practical quantification of tolerable uncertainty will become commonplace as our understanding of how to achieve it grows.

Read-across also has the potential to support several upcoming opportunities. One is its improved integration into non-animal chemical safety assessment, enabling the evaluation of One Health (the interrelationship between human and environmental adverse effects) [39]. The current paradigm is read-across of individual effects; this could be extended by incorporating knowledge of cross-species groupings. There is already a need to extend the approach beyond single definable chemicals. Grouping for nanomaterials is well-established [40], and many read-across predictions are made for UVCBs (see, e.g., ECHA guidance [41]; Prussia et al. [42]) and botanical mixtures [43]. Further areas of opportunity are to solve upcoming problems for industry and regulators in the evaluation of data-poor substances, as has been demonstrated for N-nitrosamine impurities [44], potential endocrine disruptors [45] per- and polyfluoroalkyl substances (PFAS) [46], amongst others, as well as macromolecules such as mycotoxins [47], proteins, food enzymes and genetically modified organisms (GMOs) [48].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Mark Cronin: Conceptualisation; Writing – original draft. **Terry Schultz**: Conceptualisation; Writing – review and editing.

Data availability

No data was used for the research described in the article.

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