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Towards AOP application – Implementation of an integrated approach to testing and assessment (IATA) into a pipeline tool for skin sensitization

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ABSTRACT

Since the OECD published the Adverse Outcome Pathway (AOP) for skin sensitization, many efforts have focused on how to integrate and interpret nonstandard information generated for key events in a manner that can be practically useful for decision making. These types of frameworks are known as Integrated Approaches to Testing and Assessment (IATA). Here we have outlined an IATA for skin sensitization which focuses on existing information including non testing approaches such as QSAR and read-across. The IATA was implemented into a pipeline tool using OASIS technology to provide a means of systematically collating and compiling relevant information which could be used in an assessment of skin sensitization potential. A test set of 100 substances with available skin sensitization information was profiled using the pipeline IATA. *In silico* and *in chemico* profiling information alone was able to correctly predict skin sensitization potential, with a preliminary accuracy of 73.85%. Information from other relevant endpoints (e.g., Ames mutagenicity) was found to improve the accuracy (to 87.6%) when coupled with a reaction chemistry mechanistic understanding. This pipeline platform could be useful in the assessment of skin sensitization potential and marks a step change in how non testing approaches can be practically applied.
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1. Introduction

Skin sensitization is an endpoint that has been well studied over many decades. The chemical and biological pathway driving the induction and elicitation of allergic contact dermatitis is relatively well understood (see Lepoittevin et al., 1997; Smith Pease, 2003; Adler et al., 2011; Basketter et al., 2012). This understanding was in part brought about by social and regulatory drivers particularly in EU. The principal regulatory driver to help build momentum in the pursuit of non alternative animal methods for endpoints such as skin sensitization was the 7th Amendment to the Cosmetics Directive (EU, 2003). In parallel, with the advent of the REACH legislation there was a call for alternative approaches to be used in lieu of animal testing to address the information requirements (EC, 2006). (Q)SARs and chemical category approaches were emphasized in particular (ECHA, 2008). In the run up to REACH entering into force, there was much debate and discussion about how to assure the validity of (Q)SARs with reference to the OECD Validation Principles (OECD, 2004). This included characterizing (Q)SARs and their applicability domains in terms of assessing the relevance and validity of a given (Q)SAR prediction (Netzeva et al., 2005). One approach proposed for addressing the domain of applicability for skin sensitization (Q)SAR approaches was through the use of reaction chemistry domains – a concept that was underpinned by the understanding of the chemical basis of skin sensitization itself. Aptula et al. (2005) devised 5 reaction mechanistic domains for skin sensitizers. In Aptula and Roberts (2006), this was outlined as generalized reaction chemistry principles. These principles have since been evaluated and assessed with respect to many different skin sensitization datasets (see Roberts et al., 2007a,b). The approach outlined by Roberts et al. (2007a) also discussed the need for generating reactivity information to quantify the reaction rate constant as this would be a necessary parameter in the prediction of skin sensitizing potency in addition to its potential. These reaction domains were subsequently implemented into software tools such as Toxtree (Enoch et al., 2008) for ease of use. The alerts and associated mechanistic rationales have also been implemented into both the OECD Toolbox as protein binding alerts and within the TIMES-SS hybrid expert system (Dimitrov et al., 2005). The reaction domain approach has also

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been exploited to derive new Quantitative Mechanistic Models (QMMs). QMMs are available for the following reaction domains – SNAr (Roberts et al., 2011; Roberts and Aptula, 2014), Schiff Base (Roberts et al., 2006) and Michael acceptor domains (Roberts and Natsch, 2009). A tactical strategy on how mechanistic read-across can be undertaken for the skin sensitization endpoint has also been outlined in more detail in Roberts and Patlewicz (2009) and Roberts et al. (2008).

During this time, the OECD Toolbox was undergoing extensive development with SARs encoded as profilers to facilitate the endpoint grouping of chemicals in a more efficient and systematic manner. While skin sensitization proved to be a convenient endpoint for such information to be encoded and for read-across to be performed through the derivation of chemical categories or analog approaches, a growing need was to evolve the OECD Toolbox to be capable of supporting other more complex endpoints such as repeated dose and repro-developmental toxicity. A question frequently posed was how the underlying mechanistic knowledge of a particular endpoint could be more systematically represented to facilitate a grouping approach and its associated robust read-across. Schultz et al. (2006) outlined a conceptual framework of utilizing reactivity information for more than just skin sensitization endpoints. Adverse Outcome Pathways (AOPs) and their role in helping to formulate mechanistically relevant chemical categories was the topic of discussion at the Organization for Economic Cooperation and Development (OECD) Workshop on "Using Mechanistic Information in Forming Chemical Categories" in December of 2010 (OECD, 2011). Przybylak and Schultz (2013) described how AOPs could be constructed to help structure the development of future QSARs and chemical categories to address more complex endpoints. Ankley et al. (2010) summarized the notion of AOPs in their landmark paper which described AOPs as a construct for representing existing knowledge concerning the causal linkages between initial molecular events and an adverse outcome at the individual and population level. In many ways this framework mirrors the Mode of Action (MOA) approach endorsed by the World Health Organization (WHO) (Meek et al., 2013). The AOP concept has since been taken up more broadly by the OECD to develop AOPs that can be potentially applied for different regulatory purposes.

As a proof of principle, the existing knowledge for skin sensitization proved to be an ideal case study to illustrate how an AOP could be constructed (OECD, 2012). What remains less evident is how an AOP could or should be practically applied. For skin sensitization, having a means of anchoring test methods already available or in development against key events within the published AOP in conjunction with non testing approaches is proving to be a valuable first step in defining the context of different pieces of information to ensure that a meaningful weight of evidence (WoE) assessment as part of an integrated approach to testing and assessment (IATA) can be undertaken.

One activity under the OECD umbrella involves exploring how IATA for skin sensitization might be developed and evaluated using the AOP as the underlying framework. Another has implemented the AOP for skin sensitization into the OECD Toolbox for use in chemical categorization and read-across (OECD, 2014).

Since the publication of the AOP for skin sensitization, there have been many efforts to outline conceptually what an integrated testing and assessment approach may represent. Basketter et al. (2013) summarized the outcomes from a workshop focused on moving forward with non animal testing strategies. Jaworska et al. (2013) exploited Bayesian approaches to integrate different sources of information such as different *in chemico*, *in vitro* test methods as well as measures of bioavailability to derive a probability of a chemical being a skin sensitizer in the LLNA. Rorije et al. (2013) developed an ITS under the auspices of EU OSIRIS programme which focused on a battery of expert systems that could predict likely skin sensitization potential. Kleinstreuer et al. (2014) investigated the feasibility of how new and emerging technologies such as the high throughput screening (HTS) assays utilized within the EPA's Toxcast™ programme could be anchored to key events in the skin sensitization AOP to facilitate novel Quantitative Activity Activity relationship (QAAR) model development.

The dogma is that a battery of assays will be required to assess skin sensitization potential and potency rather than a sole assay. We would propose that the exact makeup of information will be chemical and context specific. Chemical specific since an appreciation of the chemistry is needed before undertaking certain test methods and context specific since not all decisions warrant the same level of scientific confidence. The level of scientific confidence needed for the prioritization of large numbers of chemicals will be different than the scientific confidence for a risk assessment decision for a single chemical. Indeed, for some chemicals, a (Q)SAR approach in conjunction with read-across may suffice and result in a prediction of high confidence whereas in other cases, additional downstream event information might be merited depending on the end purpose and hence the level of uncertainty that can be tolerated.

This framework has built upon our previous research on TIMES-SS (Dimitrov et al., 2005; Patlewicz et al., 2007) to outline both a conceptual roadmap of evaluating and assessing skin sensitization potential and potency and the progress we have made in implementing this framework into a pipeline tool using OASIS technology that could be used to help evaluate substances more systematically.

We have taken a test set of 100 substances from the publication by Teubner et al. (2013) to illustrate the overall performance of the OASIS pipeline and a selection of substances as published in Natsch et al. (2013) to exemplify how the different outcomes can be integrated and interpreted to make a hazard determination.

2. Materials and methods

Fig. 1 proposes an overall IATA for skin sensitization. This workflow aims to capture the types of considerations when evaluating a substance for its sensitization potential. The first step considers the physical form. If a substance is a gas then inhalation exposure rather than dermal exposure will dictate the relevant route of entry. Substances which are gases at ambient temperature such as hexafluoropropene (HFP) or dimethyl ether (DME) may be justifiably excluded from specific standard sensitization testing for regulatory purposes on account of exposure considerations. This is indeed a possibility under the EU's REACH (ECHA, 2008). Substances that are corrosive or possess high acidity or basicity potential based on their pH values may also be excluded from testing. Evidence of corrosivity from a skin irritation or dermal acute study could obviate specific skin sensitization testing. This is also specified in the integrated testing strategy (ITS) for skin sensitization as outlined in the REACH guidance (ECHA, 2008). For example, testing a substance such as sulfuric acid, a known skin corrosive for its sensitization potential *in vivo* would not be scientifically meaningful. That said, it should be noted that corrosive substances (especially those identified by *in vitro* methods) should not be automatically excluded from further consideration for their skin sensitization potential and potency. A substance that is corrosive under neat conditions might not necessarily be corrosive under use conditions and some corrosives might actually be clinically relevant sensitizers, for example methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI).

Gathering available existing sensitization information is the logical next step; if a good quality sensitization study *in vivo* were

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