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

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ABSTRACT

Since the publication of the Adverse Outcome Pathway (AOP) for skin sensitisation by the OECD in 2012 [1], a number of activities were initiated on how best to integrate and interpret non-standard information generated for key events (KEs) in a manner that can be practically useful for decision making. The types of frameworks to facilitate these processes are known as Integrated Approaches to Testing and Assessment (IATA). Here we have outlined an IATA for skin sensitisation 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 sensitisation potential. A test set of substances with available skin sensitisation information taken from Tautenhahn et al. [2] was used to demonstrate the potential of an IATA. For the majority of the test set chemicals, in silico and in chemico profiling information was found to be sufficient to conclude on likely skin sensitisation potential, with a preliminary accuracy of 73.85%. Information from other relevant endpoints (e.g. Ames mutagenicity) was found to improve the accuracy further (to 87.6%) when coupled with a reaction chemistry mechanistic understanding. This Pipeline platform could be useful in the assessment of skin sensitisation potential and marks a step change in how non testing approaches can be practically applied.

INTRODUCTION: Development of an AOP

Skin sensitisation is a well studied endpoint - well characterised at all levels of biological organisation. The OECD published the AOP for skin sensitisation in 2012 [1].

1. Dock the OECD Toolbox to access available in vivo sensitisation data
2. Physical form - what are the relevant physicochemical properties - such as vapour pressure, pKq, LogKaw, MW that could play a role in limiting testing from a practical perspective?
3. Skin irritation/corrosion experimental data and predictions from specific TIMES model - is the substance corrosive – and will this impact its sensitisation potential?
4. Protein binding alerts from the OECD Toolbox and from specific profilers developed on KE data from the DRPA, GSH which characterise electrophilic reactivity?
5. Simulation of potential degradates formed from autooxidation or through metabolism
6. TIMES-SS predictions
7. Experimental data from in vitro chromosomal aberration and Ames tests – provides complementary MIE information
8. TIMES models for the in vitro chromosomal aberration and Ames tests
9. Other KE information from in chemico/in vitro assays

To test out the practical utility of the IATA-SS Pipeline, a dataset of 100 substances taken from ref.[2] were taken and profiled within the Pipeline.

RESULTS

Of the 100 substances, 3 were found to be inorganic and out of scope of the AOP and its associated IATA. 24 were found to have experimental in vivo data within the OECD Toolbox and 8 were flagged as having physicochemical properties (LogKaw) that were "extreme" [3x or >8]. The remaining 65 substances were processed through the remainder of the pipeline. Using the components characterising reactivity and the TIMES-SS model itself – a sensitivity of 74.1%, specificity of 73.7% and accuracy of 73.85% resulted for the 65 substances. There were 17 incorrect predictions with 7 apparent false negatives and 10 false positives. Each of these were evaluated in turn to identify what refinements were merited within the pipeline.

From such evaluations, the number of FNs was reduced to 3 and the number of FPs to 5. This resulted in an improved accuracy of 87.6%.

None of the 65 substances were associated with any specific in vitro/in chemico data, as such several examples were taken from Natsch et al. [3] to illustrate how the IATA-SS could be used to guide a WoE for skin sensitisation.

METHODS - Translating the IATA into a practical Pipeline

Using the components characterising reactivity and the TIMES-SS model itself – a sensitivity of 74.1%, specificity of 73.7% and accuracy of 73.85% resulted for the 65 substances. This exercise demonstrated that the use of in silico testing approaches whether it be in silico based or using rules extracted from WoE assay information do go some way to conclude on sensitisation potential and highlights how IEC information in a valuable and reasonable predictor of skin sensitisation hazard. A handful of substances that were taken from Natsch et al. [3] to illustrate how the information from IATA-SS pipeline components can be evaluated in a guided WoE approach.

CONCLUSIONS

Evaluating the skin sensitisation potential of a substance relies on different information. Here an IATA has been developed to mimic a WoE. Flow of how available existing information is used to appropriately based on QSAR approaches can be used. A software pipeline using OASIS technology enabled IATA-SS has been cross- evaluated using many of the workflow components [2]. Each of the components is underpinned by a strong mechanistic basis. Using the dataset published by Tautenhahn et al. [2], based on the protein binding alerts and TIMES-SS predictions, correct predictions of likely sensitisation potential was possible for the majority of substances. There were a number of apparent false positives and false negatives and these were considered in turn to determine what extent further refinements were needed in the IATA-SS itself. The exercise demonstrated that the use of in silico testing approaches whether it be in silico based or using rules extracted from WoE assay information do go some way to conclude on sensitisation potential and highlights how IEC information in a valuable and reasonable predictor of skin sensitisation hazard. A handful of substances that were taken from Natsch et al. [3] to illustrate how the information from IATA-SS pipeline components can be evaluated in a guided WoE approach.

METHODS: Developing an IATA for SS and translating it into a practical Pipeline

An IATA was constructed with a strong focus on mechanistic chemistry considerations for the interpretation of existing sensitisation information and to inform the generation of new test. The elements of the conceptual IATA were then translated into a software tool using OASIS Pipeline technology.

REFERENCES


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4-Nitrotoluene-2-sulfonic acid [121-03-9] gave rise to no alerts but was associated with a positive Ames result which does lend credibility to the potential for electrophilic potential and hence might be an indicator of sensitising potential. The following scheme was outlined.

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