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Weight factors in an Integrated Testing Strategy using adjusted OECD principles for (Q)SARs and extended Klimisch codes to decide on skin irritation classification

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ABSTRACT

The Integrated Assessment Scheme (IAS) defines weight factors for each piece of toxicological information under REACH in an Integrated Testing Strategy. This IAS is illustrated on skin irritation for Classification and Labelling (C&L) for five substances and using mostly (Q)SAR models. The models are the BfR Rulebase, Derek for Windows and TOPKAT, read across and pH-rules. The weight factors derived in the IAS show that for peracetic-acid and pentabromodiphenylether the C&L decision could be easily made. For bisphenol A additional information on read across was used to finalise a decision on C&L, while for methylphenyl-diisocyanate additional expert judgement was needed. For allylheptanoate only the TOPKAT prediction was in the applicability domain, which was insufficient on its own. Therefore, other non guideline testing information was used and *in vitro* testing results. The above examples on skin irritation information show how the IAS can aid in the decision making process and how it adds to the ToxRTool and the ITS of Hoffmann et al. on the same endpoint and similar methods.

1. Introduction

Within REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Integrated Testing Strategies (ITS) are proposed to use all data available for reaching a decision on Classification and Labelling (C&L) (EC, 2008a) and for risk assessment for human health endpoints in order to replace, reduce, and refine further animal testing (EC, 2006).

To achieve this goal an Integrated Testing Strategy (ITS) is provided in the REACH guidance on skin irritation (EC, 2008b). Firstly, all available toxicological data is to be gathered and needs to be assessed with regard to its utility for skin irritation hazard assessment. If these data are insufficient for drawing a conclusion on C&L further information is needed and e.g. (Quantitative)Structure Activity Relationships ((Q)SARs) on skin irritation can be run. In case the (Q)SAR prediction does not result in a final decision, *in vitro* testing for corrosion, using e.g. the *in vitro* membrane barrier test method for skin corrosion (e.g. OECD Test Guideline (TG) 435, 2006) can be carried out. When the substance is not corrosive an *in vitro* test for skin irritation can be performed using the *in vitro* skin irritation: reconstructed human epidermis model test (EC, 2009).

Despite the ITS in the REACH guidance document, still much expert judgment is needed to make a Weight of Evidence (WoE) approach on how: (i) to integrate skin irritation information from different sources and (ii) to define weight factors for each piece of toxicological information, in such an ITS. Risk assessors from Industry will need to outline the ITS's for C&L carefully to make their decision transparent for the presence, but even more so for the absence of C&L (EC, 2008a), because only substances which are classified and labelled need a chemical safety assessment under REACH (EC, 2006). Though expert judgement remains crucial for the evaluation of information, we think that, some expert judgment on skin irritation information from different sources can be categorised into weight factors and can be integrated to make the ITS more coherent and transparent.

We have developed an evaluation tool, the Integrated Assessment Scheme (IAS), which applies weight factors to each piece to skin irritation information in an ITS for C&L under REACH and the weight factor will be partly based on the reliability of the test information of a substance (EC, 2008a).

For a decision on the reliability of test information, the Klimisch codes are already used for years in the International Uniform Chemical Information Database (IUCLID) (Klimisch et al., 1997), and the fifth version is also the database under REACH (IUCLID5, EC, 2006). These Klimisch codes can be summarised as: (1) reliable without restriction, the test result is generated in compliance with an internationally accepted testing guideline (e.g. OECD test guidelines, GLP and QA statements) and is fully documented; (2) reliable

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with restriction, the test result is not generated in compliance with a testing guideline but is well documented and scientifically valid; (3) reliability is insufficient, the test is not performed according to regulatory accepted methods and; (4) reliability is not assignable, documentation is insufficient.

The Klimisch codes are developed for guidelines type and similar studies and now under REACH will need to be applied to substance information, which may come from other than guideline type of methods e.g. (Q)SARs, read across, *in vitro* and *in vivo* methods when entered into IUCLID5. Risk assessors that need to evaluate this type of information and affix a reliability code will also need to assess the ('scientific validity' of) the methodologies where the information is obtained from. This methodology assessment is recognised in the REACH legislation for (Q)SARs and implemented in Annex XI (EC, 2008b, 2006). Besides the evaluation of the substance specific test information and its methodology, the risk assessor will also need to assess the applicability of the information for C&L (and risk assessment) according to this Annex XI, especially when other than guideline methods are used. The IAS will integrate these three elements for skin irritation assessment under REACH.

For the evaluation of the reliability of the substance information, validity of methods and the REACH requirements, evaluation criteria are needed. For the evaluation of (Q)SARs predictions and (Q)SAR methodology the OECD principles for the validation of (Q)SAR can be used, which require information on the following subjects: (1) the defined toxicological endpoint; (2) the methodology; (3) the applicability domain; (4) the uncertainty or predictivity and; (5) the Mode of Action (ECB, 2008b; OECD, 2004, 2007).

In the present paper the subjects of these (Q)SAR principles will be used in the IAS to document and evaluate single pieces of skin irritation information from different methods in a coherent way to classify substances for skin corrosion, irritation or the absence of classification. We will mainly use examples of (Q)SARs, but also structural analogues and *in vitro* information are used to finalise the decision on skin irritation C&L for five substances.

In addition, the position of the IAS as an evaluation tool for other hazard endpoints will be discussed and this tool will be compared with the (a) OECD guidance on the 'Validation and international acceptance of new or updated test methods for hazard assessment' (OECD 34, 2005); (b) the ToxRTool which provides a tool for the reliability and relevance assessment of *in vitro* and *in vivo* toxicological information (Schneider et al., 2009) and (c) the general ITS for skin irritation C&L using (Q)SARs and *in vitro* data (Hoffmann et al., 2008), using allylheptanoate as an example.

2. Method

The newly developed Integrated Assessment Scheme (IAS) is an evaluation tool which defines three modules for each piece of skin irritation information independent of the source of information. These modules represent the actual test information, the methodology the information is obtained from and the regulatory need of the information.

For the evaluation of each module a standard set of evaluation principles (key principles for evaluation) will be used for information from different sources and are derived from the OECD (Q)SAR principles for (Q)SAR methods and predictions (OECD, 2004, 2007).

In the first module the endpoint and the actual result of the substance information is presented, how the methodology is applied to the specific substance and the uncertainty of the result. The assessment of the second module on the methodology, the substance information is obtained from, has become especially important under REACH, because other than guideline methods can be used for which less standardised documentation is present and which may have higher uncertainties compared to guideline studies. The general regulatory acceptance of guideline studies shows the importance of documentation and standardisation of methodologies for chemical risk assessment. In the third module the risk assessor defines what is specifically needed under REACH for a particular substance e.g. what is the actual endpoint, which method can be used (*in vivo* or *in vitro* information), which uncertainty is allowed and what type of effects need to be covered at which tonnage band.

The documentation of the three modules using the five key principles for evaluation results in a 3×5 matrix for each type of skin irritation information and is the first part of the IAS. An example of such a matrix can be found in Table 1 where skin irritation data from the OECD TG 404 for C&L is outlined.

The information of the matrix can then be used to decide upon the reliability of the information, the validity of the methodology and the regulatory need and is the second part of the IAS. In the first module an assessment code, the same as the reliability of Klimisch et al. (1997) can be affixed depending on the information available in the matrix.

2.1. The 'reliability' of substance specific information

Assessment code R1 for reliability is affixed to skin irritation information fully in accordance with methodology defined within regulatory guidelines. An example is the result from an OECD TG 404 test, which is fully in compliance with that test guideline. Also

Table 1
The IAS for substance information from the OECD TG 404 test to assess the C&L for REACH using three modules and five key principles for evaluation.

Key principles for evaluation	Module 1 The 'reliability' of the substance information	Module 2 The 'validity' of the method used to obtain this information	Module 3 The REACH 'need' of the information
Defined endpoint	Skin irritancy as defined in the method	Skin irritancy as defined in this guideline	Skin irritancy to allow for C&L
Methodology	Compare the methodology in the test report of the substance with test guideline	Type and number of test animals, amount of substance, exposure duration. Lesions: necrosis, redness and oedema, reversibility of observed effects	The substance specific information from the OECD TG 404 fulfils the REACH need for C&L
Applicability domain	Do the substance characteristics fit in the domain of the method?	All substances	Does the substance need to be assessed under REACH?
Uncertainty	The uncertainty is acceptable when OECD TG 404 is used	Internationally acceptable method, therefore uncertainty is acceptable	Uncertainty is acceptable because it is an OECD TG 404 test
Mechanistic reasoning	The substance specific MoA causes the absence or presence of effect	MoA = necrosis, damage or other effects to the skin and its persistency including metabolites of the substance	The MoA covered in the skin *in vitro* corrosion and irritation test
Assessment code	R1	V1	N1

REACH C&L (EC, 2008a); Mode of Action (MoA = result of bioavailability, chemical reactivity and biological mechanisms); R1 = reliable without restriction; V1 = valid without restriction; N1 = need without restriction.