Background

Michael acceptors are well recognised as an important chemical class of potential skin sensitisers. However not all chemicals able to undergo Michael addition reactions in conditions utilised in synthetic organic chemistry are demonstrable skin sensitisers, and some initially unreactive compounds may be metabolised, hydrolysed or oxidised to sensitising Michael acceptors. This is reflected in the relatively complex scopes of skin sensitisation alerts in the knowledge based toxicity prediction system Derek Nexus (Lhasa Limited). The allowed substituents have been earlier derived by considerations of Michael addition reactivity and sensitisation potential has been reviewed. Some initially unreactive compounds may be metabolised, hydrolysed or oxidised to conditions utilised in synthetic organic chemistry are demonstrable skin sensitisers, and skin sensitisers. However not all chemicals able to undergo Michael addition reactions in

References

Impact on Alert Performance

- addition mediated human skin sensitisation [1], requiring our critical evaluation. In carbon, and precursors included based on potential routes involving oxidation, beta-(Lhasa Limited). The allowed substituents have been earlier derived by considerations of Michael addition reactivity and sensitisation potential has been reviewed. Some initially unreactive compounds may be metabolised, hydrolysed or oxidised to conditions utilised in synthetic organic chemistry are demonstrable skin sensitisers, and skin sensitisers. However not all chemicals able to undergo Michael addition reactions in

Conclusions

- three new alerts were implemented to capture the different behaviour of subclasses of Michael acceptor – cyanoacrylate, maleimide and cyclopropenone. The revised set of Michael acceptor skin sensitisation alerts shows improvement both in accuracy and sensitivity of qualitative predictions (94% vs 78% sensitivity across identified Michael acceptors), and in accuracy of quantitative predictions. Review of available data and mechanistic knowledge (both chemical and toxicological) have allowed the alerts for skin sensitisation to be better supported. This work shows that care is required in the inclusion of potential precursors; it is important to test their in vivo relevance and appreciate the reduction in potency that may result from partial reduction of the reactive function.

Future work includes the review of heteroatom substituents on acetal/ketal/orthoester oxygens, since hydrolysis to a carbonyl carbon double bond, e.g. ruling out enol and enamine structures which would tautomerise to a predominant non-Michael reactive form.

Results

The scope of each of the eight principal alerts has been comprehensively overhauled, and those subclasses of compound (cyanoacrylates, maleimides and cyclopropenones) were additionally separated into new alerts. The process and results of this can be demonstrated with Derek alert 480; α,β-unsaturated ketones and precursors. Figure 2 shows the changes made (subject to identified Michael alerts), and in accuracy of quantitative predictions. Review of available data and mechanistic knowledge (both chemical and toxicological) have allowed the alerts for skin sensitisation to be better supported. This work shows that care is required in the inclusion of potential precursors; it is important to test their in vivo relevance and appreciate the reduction in potency that may result from partial reduction of the reactive function.

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Methods

The eight principal Michael acceptor alerts (α,β-unsaturated aldehyde, ketone, ester, amide, nitro, nitrite, imine and sulphone) in the Derek Nexus Knowledge Base vs. 2015 v. 0, were critically reviewed for this purpose we employed both member-donated and publically-available human case (study reports and maximisation tests), animal (LLNA, GPMT and variants thereof) and in vitro (e.g. DPRA, h-CLAT) data. Use was additionally made of the results of recent chemical studies of relevant Michael addition reactions and potential competing reactions (e.g. 2-5). Some work was also made of general chemical considerations such as the need for an electrophilic carbon-β-unsaturated ketones and precursors. Figure 2 shows the changes made (subject to identified Michael alerts), and in accuracy of quantitative predictions. Review of available data and mechanistic knowledge (both chemical and toxicological) have allowed the alerts for skin sensitisation to be better supported. This work shows that care is required in the inclusion of potential precursors; it is important to test their in vivo relevance and appreciate the reduction in potency that may result from partial reduction of the reactive function.

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Precursors?

- Compounds that are easily transformed or metabolised into known sensitisers (pre/pro-haptens), are typically included in Derek Nexus alerts. Earlier published studies [7,8] suggested that beta-elimination reactions of β-halo carbonyl compounds could produce unsaturated Michael substrates in the skin [9]. However, these studies were performed using an unusual test system (α-methylene-γ-lactones) in non-physiological test systems, and there is a lack of relevant supporting chemical examples showing activity across a range of assays and in man [1]. In addition, many not all of these have alternative mechanisms of toxicity, normally direct S₉₂ reactivity – thus these compounds will still be correctly predicted as sensitising – and these factors led us to remove these compounds from the alert scope, greatly simplifying the presentation. Thiokeats and fully cyclic ketals were also removed because of lower published hydrolysis rates than acylic (oxy-)ketals.

Impact on Alert Performance

The effect of the changes to the 8 principal Michael acceptor (M.A.) alerts was assessed using our compilation of skin sensitisation datasets, which contains most recently available published experimental data and human reports. A 16% increase in sensitivity (to 94%) and 10% in accuracy was indicated, for compounds considered to be Michael acceptors, and a 2% gain in specificity across the whole spectrum of skin sensitisation alerts. Figure 3 gives examples of compounds affected by these changes. Recent versions of Derek Nexus (2015.1 and subsequent) have included a quantitative EC3 prediction module based on extrapolation from similar compounds with the same toxicophore [10]. Reclassification along mechanistic lines (Figure 3, bottom left and right, e.g. removing diphenylcyclopropenone (Figure 3, bottom right) from the α,β-unsaturated ketone alert into its own alert) has improved performance of this model for the Michael acceptors. In the case of diphenylcyclopropenone, its extreme EC3 of 0.0003% was causing severe overprediction of the potency predicted for any α,β-unsaturated ketone, something which has now been resolved.

Previous false negatives, now correctly predicted

- M.A. now correctly identified (moved from other alerts) Previous false positives, now correctly negative

- Non-M.A. removed, but fire other alerts

Figure 3: Examples compounds for which Derek Nexus performance has been improved

References

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Future work includes the review of heteroatom substituents on acetal/ketal/orthoester oxygens, since hydrolysis to a carbonyl carbon double bond, e.g. ruling out enol and enamine structures which would tautomerise to a predominant non-Michael reactive form.

In silico prediction of the skin sensitisation potential of non-quinonoid Michael acceptors: new reaction assessments and evidence based precursor selection review. The process and results of this can be demonstrated with Derek alert 480; α,β-unsaturated ketones and precursors. Figure 2 shows the changes made (subject to identified Michael alerts), and in accuracy of quantitative predictions. Review of available data and mechanistic knowledge (both chemical and toxicological) have allowed the alerts for skin sensitisation to be better supported. This work shows that care is required in the inclusion of potential precursors; it is important to test their in vivo relevance and appreciate the reduction in potency that may result from partial reduction of the reactive function.

Future work includes the review of heteroatom substituents on acetal/ketal/orthoester oxygens, since hydrolysis to a carbonyl carbon group cannot be presumed.