

# A Comparison of the Michael-Type Mechanism for Mutagenicity and Skin Sensitisation



S. J. Enoch\*, Y. Koleva, M. Hewitt, J. C. Madden, M. T. D. Cronin  
School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool, UK

## Introduction

- $\alpha,\beta$ -unsaturated chemicals can potentially undergo Michael type reaction with sulphur or nitrogen in proteins or nucleic acids
- Two sets of rules have been presented previously for the identification of such chemicals, one for skin sensitisation and the second for mutagenicity<sup>1,2</sup>
- Both sets of rules suggest toxicity is related to intrinsic reactivity of the  $\alpha,\beta$ -unsaturated moiety. This mechanism is thought to occur via nucleophilic attack at the  $\beta$ -carbon (Figure 1)



Figure 1: Nucleophilic attack at the  $\beta$ -carbon

- Hexenal and cinnamaldehyde (shown in Figure 2) are both moderately strong skin sensitisers<sup>3</sup>. However only hexenal is mutagenic<sup>4</sup>

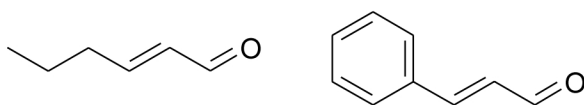


Figure 2: Hexenal and cinnamaldehyde

## Aim

- The aim of this study was to highlight the importance of the applicability domain for related mechanisms across different endpoints

## Methods

- Skin sensitisation and mutagenicity data were collected for a series of 45 aldehydes and ketones<sup>2,3,5</sup>
- Hexenal and cinnamaldehyde were selected for the initial mechanistic comparison
- Both chemicals were classified according to the reactivity rules for both skin sensitisation and mutagenicity
- Mechanistic evaluation was undertaken to investigate the results

## Acknowledgements

The funding from the European Union 6th Framework CAESAR Specific Targeted Project (SSPI-022674-CAESAR) is gratefully acknowledged

## Results & Discussion

- The results of the mechanistic classification are shown in Table 1

Chemical	Mutagenicity Rules	Skin Rules	Mutagenic	Skin Sensitiser
Hexenal	Michael	Michael	Yes	Moderate
Cinnamaldehyde	Michael	Michael	No	Moderate

Table 1: Classification results

- Both sets of reactivity rules correctly identify hexenal as being both mutagenic and causing skin sensitisation but incorrectly identify cinnamaldehyde as being mutagenic
- This highlights the need for careful consideration of the applicability domain for toxicophores for each endpoint
- It is likely that the differing reactivities of cinnamaldehyde with proteins and nucleic acids are due to its chemical softness. This difference could be due to the ability of cinnamaldehyde to form the adducts thought to be responsible for mutagenicity or could be due to cinnamaldehyde being chemically soft and thus not interacting sufficiently with nitrogen atoms in guanine

## Conclusion

The results of this initial investigation showed:

- Reactivity rules are useful for identifying potential reactive compounds responsible for mutagenicity and skin sensitisation
- It is of great importance that an endpoint specific applicability domain is developed for each toxicophore
- Investigations into the transition states for these reactions are on-going

## References

1. Aptula et al, Chem. Res. Tox., 2006, 19, p1097
2. Kazius et al, J. Med. Chem., 2005, 48, p312
3. Gerberick et al, Dermatitis, 2005, 16, p157
4. Eder et al, Tox. Lett., 1993, 67, p87
5. Cronin et al, SAR and QSAR Environ. Res., 1994, 2, p159

\*For information contact:  
s.j.enoch@ljmu.ac.uk