**Method, Results and Expert review**

1. **A robust structural definition for carbamates was created** (Figure 2).
2. **A dataset of compounds with Ames data were extracted from** Vinyl Nexus and queried for compounds containing a carbamate (Figure 3).
3. **Biochemically derived were removed as toxicity cannot be associated to one structural feature.**
4. **The resulting 69 carbamates were then processed through Derek and Sarah Nexus to provide (Q)SAR predictions** (Figure 1-decision matrix).

**Mechanism of action**

Urethane’s mutagenic mode of action is believed to be via vinyl carbamate (Figure 4). Analysis of the structural-activity relationships indicates that only low molecular weight derivatives of urethane may be able to proceed through this mechanism (Table 2). Published structural alerts are likely to have been derived from the activity of low molecular weight carbamate derivatives capable of forming DNA reactive epoxides, but this mechanism is not applicable to the whole chemical class.

**Carbamate protecting groups**

Mining public and proprietary data sources, including data donated by two Lhasa members, furnished small datasets for Chz, Boc and Fmoc protected carbamates (Table 3, Figure 5). Compounds which contained known toxicophores were removed to allow assessment of the carbamylate functionality only. The prevalence of mutagenic Chz, Boc and Fmoc containing carbamates is low. Only 6 out of 92 nonalerting compounds were Ames active.

**Conclusions**

- **Assessment of public and proprietary data has shown that, in general, carbamates are inactive in the Ames test, with a few notable exceptions; namely urethane and some small molecule derivatives.**
- **Subsets of the carbamate chemical class are covered in Derek and Sarah Nexus and (Q)SAR predictions perform well for this difficult area of chemical space.**
- **Addition of an alert for in vitro mutagenicity to cover the whole carbamate chemical class would be detrimental to the predictive performance of a (Q)SAR system and ultimately an ICH M7 classification by increasing time spent on expert review as well as unnecessary testing and/or control measures of impurities.**

**References**