Examining the Use of Surrogates in Combination with The Carcinogenic Potency Categorization Approach when Establishing Acceptable Intake Limits of N-Nitrosamine Impurities

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Introduction
The Carcinogenic Potency Categorization Approach (CPCA) methodology represents a significant shift in the regulatory landscape for establishing permissible intake limits for potentially carcinogenic Nitrosamine Drug Substance-Related Impurities (NDSRIs). Nevertheless, regulatory agencies still permit the use of surrogate compounds to justify higher acceptable intake (AI) limits than those predicted by the CPCA. This raises several questions: How does considering both approaches impact carcinogenicity data and its structural features, including carcinogenicity. For each NDSRI, a surrogate was only considered suitable when it had robust data on animal carcinogenicity. For AI limit calculations, regulatory agencies recommend selecting surrogates with robust carcinogenicity data. Agencies recommend that ideal surrogate nitrosamines are often unavailable. Agencies recommend using NDMA, NPIP, NNN, and NMDR as surrogates, given their robust mutagenicity and carcinogenicity data availability.

N-Nitrosamine Duloxetine

Examples

<table>
<thead>
<tr>
<th>Surrogate AI</th>
<th>Adjusted AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Nitrosoduloxetine</td>
<td>157.5 ng/day</td>
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<tr>
<td>N-nitroso-nortriptyline</td>
<td>100 ng/day</td>
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Additional Considerations: Molecular Weight Adjustments
- AI based on statistical extrapolation or analogs should be expressed in molar terms or adjusted for molecular weight (MW).
- This adjustment accounts for the fact that each nitrosim group may cause only one DNA mutation.
- The number of molecules per mass unit is directly proportional to the MW of the target substance.

When CPCA was applied to 7,679 potential NDSRIs, 21% of them were predicted to have an AI of 18/26.5 ng/day (CPCA category 1).

Results and Discussions
A dataset of 7,679 potential NDSRIs was analyzed using 195 nitrosamine surrogates, of which 10 have robust carcinogenicity data. The analysis was performed using QAM Flex v2.7. A suitable surrogate was selected when there is a 100% match of relevant structural features and carcinogenicity is robust as per Bercu et al.’s recommendations.

- Robust (tested with 1 or more dose groups, well-defined methodology, 50 animals/dose/sex, daily dosing, administered over the animal’s lifespan)
- Limited but sufficient (less than 3 dose groups, fewer than 50 animals/dose/sex, intermittent dosing, or not administered over a lifetime)
- Insufficient (single dose, exposure less than half a lifetime, single-sex, fewer than 20 animals/dose group, or mechanistic/metabolism studies)

Surrogate support was identified for 1,243 out of 1,617 NDSRIs (77%) with a CPCA AI of 400 ng/day, surrogate support was available. Only six NDSRIs could be assigned higher AI limits of 1300 or 1900 ng/day.

Conclusions
- The surrogate-based approach mainly benefits NDSRIs in potency category 1.
- Other categories gain minor advantages from this method.
- NNK, NTHP, and NMA are the most chosen surrogates.

References
2. European Medicines Agency. Appendix 1 to Questions and answers for marketing authorization holders/applicants on the CHMP Opinion for the Article 10(c) Regulation (EC) No 726/2004 on unrealistic information in human medicinal products.

Conflict of Interest: Authors are employed by MultiCASE Inc.