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

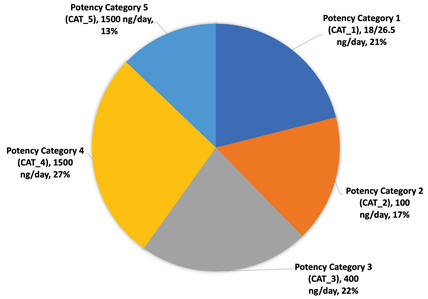
The Carcinogenic Potency Categorization Approach (CPCA) methodology represents a significant shift in the regulatory landscape for establishing permissible intake limits for potentially carcinogenic Nitrosamine Drug Substance-Related Impurities (NDSRIs). Nevertheless, regulatory agencies still permit 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 AI determination? How frequently do surrogates have different AI limits? Which surrogates are most selected in read-across studies? And perhaps most importantly, how does one choose an appropriate surrogate?

This study aims to shed light on these inquiries. We examined a dataset comprising 7,679 potential NDSRIs and 195 unique nitrosamine surrogates, 10 of which possess robust data on animal carcinogenicity. For each NDSRI, a surrogate was only considered suitable when it had robust carcinogenicity data and its structural features, including α-H counts, CPCA-based features including activating and deactivating features, perfectly match with those of the corresponding NDSRI.

Background

- N-nitrosamine impurities are a long-standing concern for their potential to form from common drugs in the stomach's acidic conditions with nitrosating agents.
- Regulatory agencies responded with revised guidance on N-nitrosamines by the EMA and USFDA in mid-2023, with the introduction of the Carcinogenic Potency Categorization Approach (CPCA) to categorize nitrosamines into discrete Acceptable Intake (AI) levels, from 18/26.5 to 1500 ng [1,2].
- CPCA focuses on NDSRIs, using structure-activity relationships (SAR) to evaluate nitrosamines based on their structural features that affect metabolic activation or clearance.
- The approach is conservative and open to revision with new scientific data.

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).



Is CPCA Call Final?

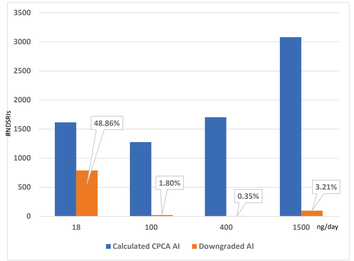
- For AI limit calculations, regulatory agencies recommend selecting surrogates with robust carcinogenicity data.
- Agencies recognize that ideal surrogate nitrosamines are often unavailable.
- Agencies recommend using NDMA, NPIP, NNK, NPYR, and NMOR as surrogates, given their robust mutagenicity and carcinogenicity data availability[1].

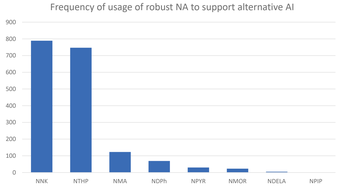
Results and Discussions

A dataset of 7,679 potential NDSRIs[3] was analyzed using 195 nitrosamine surrogates, of which 10 have robust carcinogenicity data. The analysis was performed using QSAR Flex v2.7. A suitable surrogate was selected when there is a 100% match of relevant structural features and carcinogenicity data is robust as per Bercu et al.'s recommendations[4]:

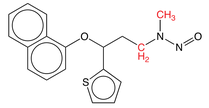
- **Robust** (tested with 3 or more dose groups, well-defined methodology, 50 animals/dose/sex, daily dosing, administered over the animal's lifespan)
- **Limited but sufficient** (less than 3 dose groups, fewer than 50 animals/dose/sex, intermittent dosing, or not administered over a lifetime)
- **Insufficient** (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-predicted AI of 18/26.5 ng/day. Of these, 790 had surrogates with an AI limit of 100 ng/day.
- For 753 out of 1704 NDSRIs (44%) 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.
- Among those with a CPCA AI of 1500 ng/day, 99 out of 3081 NDSRIs (3%) found surrogate support. Within this group, 30 NDSRIs were upgraded to an AI limit of 1700 ng/day and 69 to 116,000 ng/day.
- Not all surrogates are recognized as robust by all regulatory agencies, e.g., NMA.





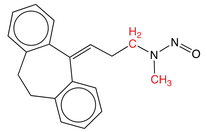
Examples



N-nitroso duloxetine

US FDA - 100 ng/day, Health Canada - 100 ng/day, European Medicines Agency - 100 ng/day

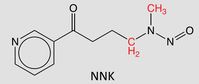
CPCA AI: 18/26.5 ng/day
Surrogate-based AI: 100 ng/day



NNORT, N-nitroso-nortriptyline

US FDA - 26.5 ng/day, Health Canada - 8 ng/day, European Medicines Agency - 8 ng/day.

CPCA AI: 18/26.5 ng/day
Surrogate-based AI: 100 ng/day



NNK

Chosen Surrogate

NNK (4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone)

TD_{50} = 0.0999 mg/kg/day (robust data)

Additional Considerations: Molecular Weight Adjustments

- AIs 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 nitroso group may cause only one DNA mutation.
- The number of molecules per mass unit is directly proportional to the MW of the target substance[5,6].

NDSRI	Surrogate	AI	Adjusted AI
N-Nitroso Duloxetine	NNK	100 ng/day	326.40/207.23*100 = 157.5 ng/day
N-nitroso-nortriptyline	NNK	100 ng/day	292.4/207.23*100 = 141.1 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

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2. European Medicines Agency. Appendix 1 to Questions and answers for marketing authorization holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products.).
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Conflict of Interest: Authors are employed by MultiCASE Inc