Development of an Updated Carcinogenicity Potency Database and Analysis of Thresholds of Toxicological Concern

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Background

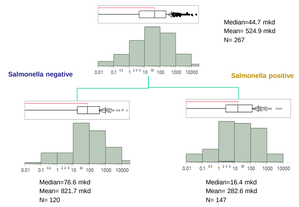
- Threshold of Toxicological Concern (TTC) is a pragmatic risk assessment tool. Determination of genotoxicity is vital to apply TTC for potential carcinogens.
- Kroes et al (2004) proposed (for compounds not in "exclusionary categories") TTC values of:
  0.025 µg/kg bw/d for non-DNA reactive mutagens and 0.0025 µg/kg bw/d for DNA reactive mutagens.
- These TTC thresholds were derived, in part at least, from the original Cancer Potency DataBase (CPDB) (https://toxnet.nlm.nih.gov/cpdb/).
- Boobis et al (2017) recognised the need to revisit and revise TTC for (genotoxic) carcinogens.

Aims of Study

- Update the CPDB to create a curated, freely available Cancer Potency TTC dataset
- Evaluate mode of action of carcinogens to identify genotoxic and non-genotoxic carcinogens
- Quantitative analysis of the database comparing TDx and BMDL methods for the Point of Departure
- Re-evaluation of TTC thresholds for cancer potency

Existing data:

- 652 chemicals from acceptable studies
- 572 carcinogens from acceptable studies
- 428 carcinogens from acceptable studies and having Ames data



Study Inclusion Criteria

Included - CPDB

- GLP studies or equivalent protocols
- Appropriate sample size (≥40)
- Exposures shorter than life time included only if results are statistically positive
- Data with incident rates

Included - TTC

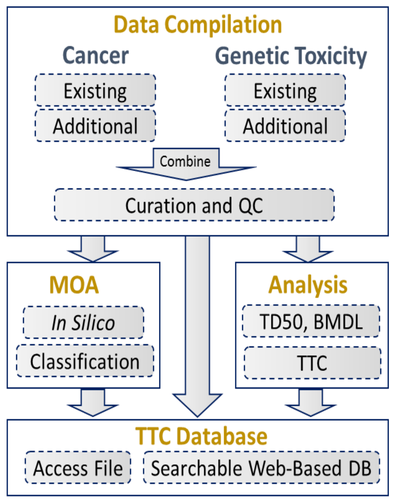
- Statistically significant dose responses
- Oral studies
- Test animals: rat, mouse, hamster, monkey, dogs

Excluded - CPDB

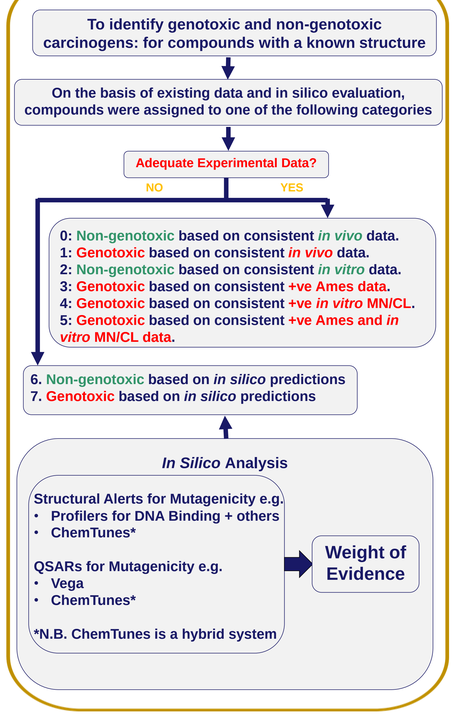
- Single dose studies

Excluded - TTC

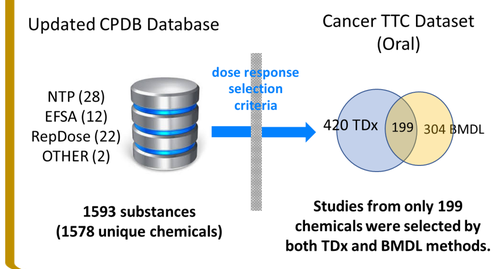
- Single dose studies
- Non-specific sites
  - TBA (all tumour bearing animals), MXA, MXB
- Mixed tumours
  - MXA, MXB, MTB, MTM, MIX, etc.
- Clear negative studies
- Studies with no / ambiguous results



MOA Strategy



New Cancer Potency Database (as of 2018)



- Transparent and robust methods were used to calculate TD25 and TD50 and to model BMDL:
  - Logistic logit method to calculate TD10, TD25 and TD50
  - PROAST program to model BMDL

BMDL

Proast models for averaging

1	two.stage
2	log.logist
3	Weibull
4	log.prob
5	gamma
6	probit
7	logistic

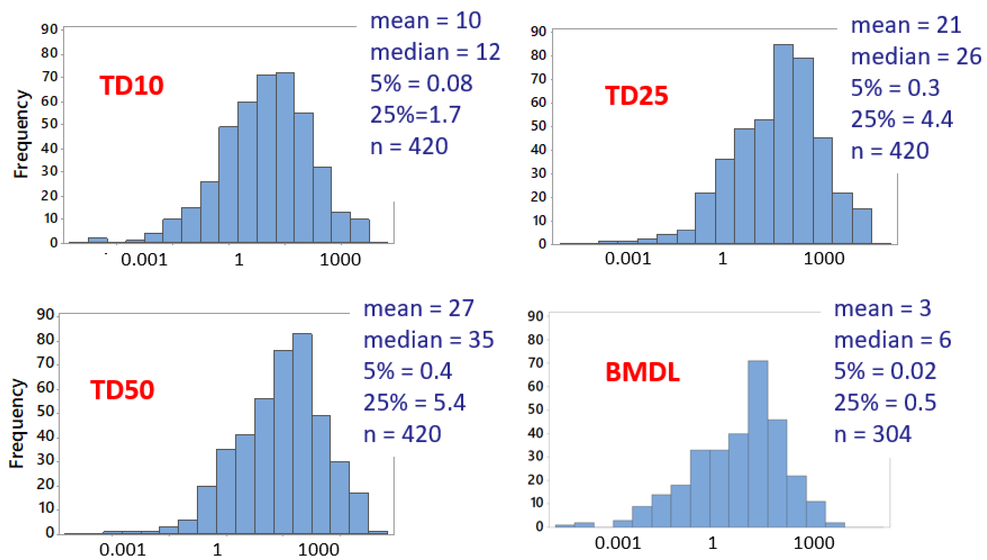
TDx Calculations

- TD10, TD25 and TD50 calculated from constructed dose-response curves
- Logistic logit function preferable to logistic log and PLS

BMDL Modelling

- Modelling of dose-response data performed to estimate the Benchmark Dose Limit (BMDL) at an BMR of 10% using EFSA approach)
- 14,936 tumour data processed

Points of Departure: Distributions



TDx and BMDL values are given in mg/kg-bw/day

Points of Departure vs Gentoxicity

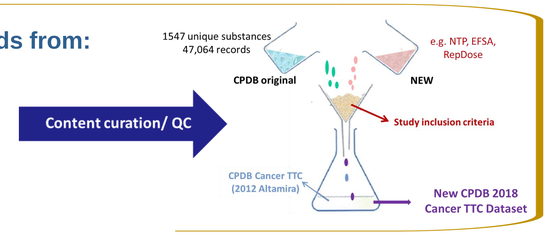
TD10	n	mean	median	5th %ile	25th %ile
Genotoxic	277	5.8	6.0	0.052	1.1
Non - Genotoxic	138	25	27	0.37	6.8
TD25	**n**	**mean**	**median**	**5th %ile**	**25th %ile**
Genotoxic	277	13	18	0.24	2.4
Non - Genotoxic	138	55	78	0.80	17
TD50	**n**	**mean**	**median**	**5th %ile**	**25th %ile**
Genotoxic	277	17	20	0.24	3.0
Non - Genotoxic	138	72	101	1.1	19
BMDL	**n**	**mean**	**median**	**5th %ile**	**25th %ile**
Genotoxic	180	2.2	4.4	0.013	0.36
Non - Genotoxic	121	4.4	6.2	0.035	0.87

Data for > 60 new compounds from:

- NTP studies
- RDT studies from RepDose

Content curation/QC:

- Chemoinformatics curation
- Toxicity study reviews



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References

- Boobis A et al (2017) *Crit. Rev. Toxicol.* 47: 710–732.
- Kroes R et al (2004) *Fd Chem. Toxicol*. 42: 65–83.