Are non-genotoxic tumorigenic substances adequatly covered in the current TTC approach?

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This study aimed to identify the most sensitive dose descriptor after chronic oral exposure for non-genotoxic carcinogens. Using the recently extended Cancer Potency Database, 232 compounds were classified as non-genotoxic carcinogens, using a straightforward decision tree. Following a detailed review of peer-reviewed publications, experimental and predicted data, the dataset was reduced to 137 organic compounds, excluding non-carcinogens, inorganic and genotoxic compounds.

NOAEL values were derived from 689 studies with repeated oral exposure (483 chronic and 206 subchronic studies) using high quality data from the RepDose, ToxRef and COSMOS databases or literature. NOAELs were compared based on either the most sensitive i) adverse apical effect in the entire study; ii) non-neoplastic lesions; or iii) neoplastic lesions. Study quality was considered as one potential confounder.

To distinguish the most sensitive point of departure for risk assessment, the study NOAELs were plotted against the effective tumour dose (ETD_{10}) and the benchmark dose level ($BMDL_{10}$) calculated by model averaging. The comparative analysis between NOAEL/EDT_{10} and $BMDL_{10}$ values revealed that bioaccumulating substances and steroids were among the 5% most toxic compounds. Exclusion of these compounds led to comparable 5th percentiles for chronic NOAELs/$BMDL_{10}$ values, whereas the 5th percentile EDT_{10} is about three times higher. A statistical significant difference was not detected.

These results were evaluated with regard to the current threshold of toxicological concern (TTC) supporting the application of Cramer Class thresholds to non-genotoxic tumorigen substances. This work received funding from the CEFIC LRI B18_2 project.