Toxicity predictions as risk assessments of food additives by *in silico* approaches

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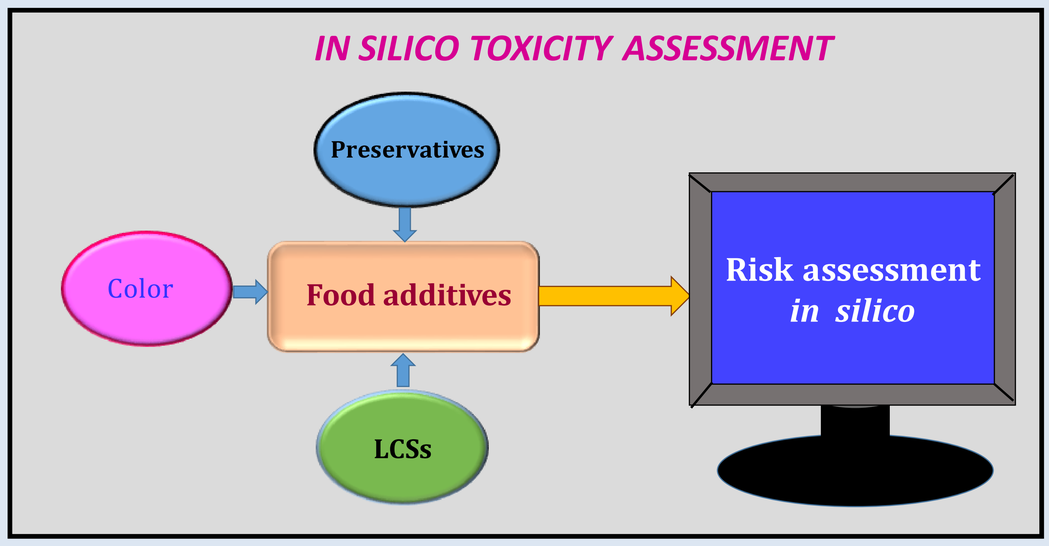
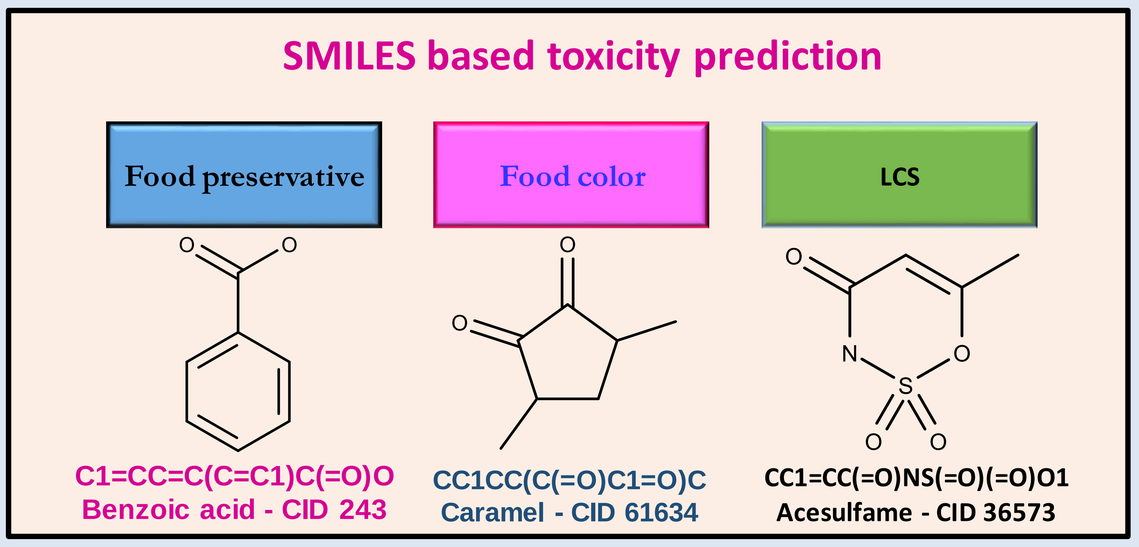
Abstract: *In silico* methodologies, such as quantitative structure-activity relationships (QSARs), allow the prediction of a wide variety of toxicological properties and biological activities for structurally diverse substances. Industrial food production brought along additives such as preservatives, food colors, and low-calorie sweeteners (LCSs). Food preservatives prevent the rotting of perishable food. Dyes are used as food additives and also in various clinical and medical applications. LCSs are increasingly replacing natural sugars as sweeteners. Such food amendments may cause human health effects particularly through their chronic consumption that need to be screened by various toxicological approaches. We used Marvin Sketch to draw the molecular structures and simplified molecular input line entry systems (SMILES) of food additives obtained from the PubChem database to evaluate their mutagenicity and carcinogenicity. The predictive tools LAZAR, pKCSM, Toxtree toxicity were used to assess the mutagenicity and carcinogenicity of selected food colors, preservatives, and LCSs based on literature surveys. The aims of this study were to predict mutagenicity and carcinogenicity of diverse food additives through different chemcomputational tools. *In silico* methods are among the most suitable tools for initial safety screening of chemicals. QSAR tools can provide useful solutions for risk assessments. They allow predictions for a large amount of structurally characterized, known or not as yet synthesized compounds, in a fast, reproducible, and relatively straightforward manner. Due to their resource- and time-saving characteristics, they are recognized as useful toxicity screening tools.

Introduction



Method



Mutagenicity prediction

Food Preservatives	LAZAR	pKCSM	Toxtree
Ascorbic acid	NM	NM	NM
Benzoic acid	NM	NM	NM
Butylated hydroxyanisole	M	NM	NM
Calcium sorbate	NM	NM	NM
Citric acid	NM	NM	M
Erythorbic acid	NM	NM	NM
Iso-Ascorbic acid	NM	NM	NM
Potassium acetate	NM	NM	NM
Propionic acid	NM	NM	NM
Sodium ascorbate	NM	NM	NM
Sodium erythorbate	NM	NM	NM
Sorbic acid	NM	NM	NM

Food color	LAZAR	pKCSM	Toxtree
Patent Blue V	M	M	M
Quinophthalone	M	NM	NM
Carmoisine	M	NM	M
Acid Green 25	M	M	M
Tartrazine	NM	NM	NM
Sunset yellow	M	NM	M
Erythrosine B	NM	NM	M
Allura red AC	NM	NM	M
Indigo carmine	M	NM	M
Brilliant blue FCF	M	M	M
Fast green FCF	M	M	M
Naphthol yellow	M	M	NM
Caramel	NM	NM	NM
Curcumin	NM	NM	NM
Annatto	NM	NM	NM

LCSs	LAZAR	pKCSM	Toxtree
Glucin	M	M	M
P 4000	M	M	M
Acesulfame	M	M	M
Advantame anhydrous	NM	NM	NM
Alitame	NM	NM	NM
Aspartame	NM	NM	NM
Neohesperidin DC	NM	NM	NM
Neotame	NM	NM	NM
Rebaudioside A	NM	NM	NM
Saccharin	NM	NM	NM
Sodium cyclamate	NM	NM	NM
Sucralose	M	M	M

Carcinogenicity prediction

Food preservatives	LAZAR			Toxtree
	Rodent	Mouse	Rat	
Ascorbic acid	C	NC	NC	NC
Benzoic acid	NC	NC	NC	NC
Butylated hydroxyanisole	NC	NC	NC	NC
Calcium sorbate	NC	NC	NC	NC
Citric acid	NC	NC	NC	C
Erythorbic acid	C	NC	NC	NC
Iso-Ascorbic acid	NC	NC	NC	NC
Potassium acetate	NC	NC	NC	NC
Propionic acid	NC	NC	NC	NC
Sodium ascorbate	C	NC	NC	NC
Sodium erythorbate	NC	NC	NC	NC
Sorbic acid	NC	NC	NC	NC

Food color	LAZAR			Toxtree
	Rodent	Rat	Mouse	
Patent blue V	NC	C	NC	C
Quinophthalone	NC	NC	NC	NC
Carmoisine	NC	C	NC	C
Acid green 25	C	C	NC	C
Tartrazine	NC	NC	NC	NC
Sunset yellow	NC	C	NC	C
Erythrosine B	NC	C	NC	C
Allura red AC	NC	C	NC	C
Indigo carmine	NC	NC	NC	C
Brilliant blue FCF	NC	C	NC	C
Fast green FCF	NC	C	NC	C
Naphthol yellow	NC	C	NC	NC
Caramel	*	*	*	NC
Curcumin	NC	NC	NC	NC
Annatto	NC	NC	NC	NC
Lycopene	NC	NC	NC	NC

LCSs	LAZAR			Toxtree
	Rodent	Rat	Mouse	
Glucin	C	C	C	C
P 4000	C	C	NC	C
Acesulfame	*	*	*	C
Advantame anhydrous	NC	NC	NC	NC
Alitame	C	NC	NC	NC
Aspartame	C	C	NC	NC
Neohesperidin DC	NC	NC	NC	NC
Neotame	NC	C	NC	NC
Rebaudioside A	NC	NC	NC	NC
Saccharin	NC	NC	NC	NC
Sodium cyclamate	NC	NC	NC	NC
Sucralose	C	C	NC	C

Conclusions

- **Food preservatives are not predicted as mutagenic in this *in silico* assessment; food color - Patent blue V, Acid green 25, Brilliant blue FCF, Fast green FCF, and Naphthol yellow are mutagenic; LCSs - Glucin, P 4000, acesulfame and sucralose are mutagenic.**
- **Food preservatives are not predicted as carcinogenic in all LAZAR rodent model. All other evaluated food preservatives are not carcinogenic. Food color - Acid Green 25 predicted as carcinogenic in LAZAR-rodent and rat model and by Toxtree.**
- **LCSs - Glucin is predicted as carcinogenic by the LAZAR and Toxtree tools. P 4000 and sucralose are predicted as a carcinogen in Toxtree and LAZAR- rodent including rat *in silico* model.**
- **These computational toxicity assessments are fast and reliable to evaluate the toxicity of known and unknown chemicals.**

Computational tools

- **LAZAR** toxicity predictions software. Available from: http://lazar.in-silico.de/predict
- **MarvinSketch 17.6** freeware for academic use, https://www.chemaxon.com/
- **pKCSM**-pharmacokinetics, accessible from http://biosig.unimelb.edu.au/pkcsm/
- **Toxtree 2.6.13** available from http://toxtree.sourceforge.net/

Abbreviations

C - carcinogenic, CID - compound Identifier, LAZAR - lazy structure-activity relationships, M - mutagenic, NC = non-carcinogenic, NM = non-mutagenic.