Table: Overview of TTC Values (October 2010)

Note: Applying the TTC concept needs a good understanding about exposure and a good knowledge of the underlying principles for setting TTC values as described in the references cited in this overview

prepared by C. Hennes / ECETOC with input from the (former) TTC Task Force (members mentioned below)

Toxicological Endpoint / Exposure Route	**TTC Level µg/person/day (unless indicated differently)**	**TTC Level µg/kg bw/day (unless indicated differently)**	**Types / Uses of Chemicals**	**Database**	**Key References**	**Comments**
Genotoxicity / oral	**1.5**	**0.025**	Food packaging migrants, flavouring agents	Carcinogenic Potency Database – CPDB: 709 carcinogens (there were 343 carcinogens in the CPDB of Gold et al at the time of FDA's original analysis; subsequently expanded to 709)	Rulis (1986, 1989); Gold et al. (1984; 1989); Cheeseman et al. (1999); Munro et al. (1999)	endorsed by US FDA and JECFA (EFSA considers endorsement) To Note: Although based on the CPDB, FDA does not accept use of this TTC for genotoxic chemicals or chemicals with structural alerts or other evidence for genotoxicity
Genotoxicity / oral	**0.15** (cohort of concern of high potency genotoxic carcinogens)	**0.0025**	Unintended (trace) chemicals in food	Carcinogenic Potency Database – CPDB: 709 see above), further substances added by Kroes et al bringing the database to 730	Kroes et al. (2004)	cohort of concern comprises aflatoxin-like, N-nitroso- and azoxy-compounds
Genotoxicity / oral	**0.15** (chemicals with structural alerts for genotoxicity; lifetime daily exposure) **1.5** (chemicals with structural alerts but negative Ames data; lifetime daily exposure)		Unintended (trace) chemicals in food	Review by Cheeseman et al of TD_{50}s for carcinogens that are Ames positive vs. Ames negative. For less-than-lifetime, literature supporting higher daily exposures for less-than-lifetime taking into account a 'dose rate correction factor'	Felter et al. (2009)	

Toxicological Endpoint / Exposure Route	TTC Level µg/person/day (unless indicated differently)	TTC Level µg/kg bw/day (unless indicated differently)	Types / Uses of Chemicals	Database	Key References	Comments
	1.5 (chemicals with structural alerts for genotoxicity; exposure < 1 yr)					
Genotoxicity / oral	**1.5** (ADI) (exposure >12 months) **10** (ADI) (exposure >6-12 months) **20** (ADI) (exposure >3-6 months) **40** (ADI) (exposure >1-3 months) **120** (ADI) (exposure ≤1 month)	**0.025**	Pharmaceutical impurities	'Scientific reasoning as described in the reference'	Müller et al. (2006)	endorsed by EMEA
Non-genotoxic carcinogenicity / oral	**1** (ADI) (likely to be carcinogenic) **10** (ADI) (likely to be potent or highly toxic) **100** (ADI) (not likely to be potent, highly toxic or carcin.)		Pharmaceutical impurities	Carcinogenic Potency Database – CPDB: 709 see above), further substances added by Kroes et al bringing the database to 730, and other databases of the pharmaceutical industry	Dolan et al. (2005); Kroes et al. (2004)	

Toxicological Endpoint / Exposure Route	**TTC Level µg/person/day (unless indicated differently)**	**TTC Level µg/kg bw/day (unless indicated differently)**	**Types / Uses of Chemicals**	**Database**	**Key References**	
Non-genotoxic / Non-carcinogenic endpoints / oral	**1.5**[1] **15**[2] **45**[3]	**0.025**	Food packaging migrants, flavouring agents	Registry of Toxic Effects of Chemical Substances (RTECS): 3306 substances tested for reprotoxicity 2542 substances tested multiple dose toxicity	Cheeseman et al. (1999)	endorsed by US FDA and JECFA
Non-carcinogenic endpoints / oral	**1800** (class I) **540** (class II) **90** (class III) (Cramer classes)	**30** **9** **1.5**	Wide range of organic chemical structures	Database of 613 organic substances: industrial chemicals, pharmaceuticals, food, agricultural and consumer substances tested for sub-chronic and chronic toxicity, teratogenicity, reprotoxicity	Munro et al. (1996)	endorsed by JECFA
Non-carcinogenic endpoints / oral (guideline studies)	**54** (sub-acute OECD 407) **84** (sub-chronic OECD 408) **38** (chronic OECD 451/452/453)		Wide range of organic chemical structures	Data on 541 chemicals of the Munro database (see above) and RepDose with 543 chemicals / 1122 repeat-dose, oral studies (100 chemicals in common)	Tluczkiewicz et al. (2009); Bitsch et al. (2006); Munro et al. (1996, 1999)	
Non-carcinogenic endpoints / inhalation (guideline studies)	**88** (sub-acute OECD 412) **12** (sub-chronic OECD 413) **17** (chronic OECD 451/452/453)		Wide range of organic chemical structures	RepDose with 255 chemicals / 590 repeat-dose, inhalation studies	Tluczkiewicz et al. (2009); Bitsch et al. (2006); Munro et al. (1996, 1999)	

Toxicological Endpoint / Exposure Route	**TTC Level µg/person/day (unless indicated differently)**	**TTC Level µg/kg bw/day (unless indicated differently)**	**Types / Uses of Chemicals**	**Database**	**Key References**	
Non-carcinogenic endpoints / inhalation	systemic effects: **980** (class I) **170** (class III) **300** (class I-III) local effects: **1400** (class I) **470** (class III) **1000** (class I-III) (Cramer classes)		Aerosol ingredients in consumer products	NOAEC or NOAEL of 92 chemicals with sub-acute, sub-chronic, chronic inhalation toxicity studies from US EPA SIDS, BfR, TNO, ECETOC	Carthew et al. (2009)	under development
Non-carcinogenic endpoints / inhalation	**180** (class I) **4** (class III) (Cramer classes)		Wide range of organic chemical structures	RepDose database (see above under 'inhalation guideline studies') but without substances with structural alerts for genotoxicity	Escher et al. (2010)	
Reprotoxicity / oral		**1.5** (fertility) **1.0** (developmental)	Range of organic chemical structures	Risk assessment reports on 91 chemicals on ECB website (58 fertility studies, 62 developmental studies)	Bernauer et al. (2008)	
Reprotoxicity / inhalation		**1.0** µg/m^3 (fertility) **0.5** µg/m^3 (developmental)	Range of organic chemical structures	Risk assessment reports on 91 chemicals on ECB website (58 fertility studies, 62 developmental studies)	Bernauer et al. (2008)	
Reprotoxicity / oral		**8** (developmental) **8** (maternal)	Range of organic chemical structures	Data from BASF studies (OECD 414) (92 maternal, 93 developmental toxicity)	Van Ravenzwaay et al. (2010)	
Neurotoxicity / oral	**18**	**0.3**	Organophosphates	NOEL of 31 organophosphorous insecticides in the Munro et al, 1996, database	Munro et al. (1999)	not universally accepted as a TTC (Kroes et al., 2004)

Toxicological Endpoint / Exposure Route	**TTC Level µg/person/day (unless indicated differently)**	**TTC Level µg/kg bw/day (unless indicated differently)**	**Types / Uses of Chemicals**	**Database**	**Key References**	**Endpoint / Exposure Route**
Acute toxicity / inhalation		**4** µg/m^3 (Cat.1) **20** µg/m^3 (Cat.2) **125** µg/m^3(Cat.3) **125** µg/m^3(Cat.4) **1** mg/m^3 (Cat.5) [Cat. = GHS Cat.]	Industrial, environmental, consumer chemicals	Database on 97 organic and inorganic chemicals	Grant et al. (2007)	
Skin sensitisation / dermal	Probabilistic method proposed to establish a DST (dermal sensitisation threshold). Level will vary according to product type and use	Suggested **1.64** µg/cm^2 for rinse-off (shampoo) **0.55** µg/cm^2 for leave-on (deodorant)	Personal care products/cosmetics	LLNA EC3 values of 167 skin sensitisers. DST proposed to be based on gamma distribution of those EC3 values.	Safford (2008)	under development; needs general agreement on probability of acceptable risk (like for probability of carcinogenic risk)
Skin sensitisation / dermal		**0.91** µg/cm^2 for typical **0.30** µg/cm^2 for unfavourable exposure conditions (e.g. penetration enhancement)	Fragrance ingredients and chemically related substances (e.g. plant extracts or flavours)	Meta-analysis of human data (HRIPT) on 53 fragrance ingredients with skin sensitisation potential in IFRA/RIFM dataset	Keller et al. (2009)	under development
Aquatic toxicity	ETNC$_{aqMOA1-3}$: **0.1** µg/l MOA1: non-polar, inert MOA2 : polar, less inert MOA3 : reactive		Wide range of organic chemical structures	PNEC of 53 chemicals in EURATS database; LC_{50} and NOEC (>600) in ECETOC EAT3 database (TR91): MOA1:127, MOA2: 122, MOA3:105; LC_{50} in US EPA Duluth database of 617 chemicals; LC50 in Utrecht Univ. database of 180 chemicals	De Wolf et al. (2005)	not yet accepted

[1]substances with positive Ames test or certain structural alerts, like N-nitroso or benzindine-like chemicals
[2]substances without structural alerts for carcinogenicity or with negative mutagenicity (Ames) test
[3]substances without structural alerts for carcinogenicity or with negative mutagenicity (Ames) test and with an appropriate acute toxicity test with LD50>1000 mg/kg bw

Note: Excluded from TTC concept (according to Kroes et al., 2004)

- heavy metals
- polyhalogenated dibenzo-p-dioxins, dibenzofurans, biphenyls
- endocrine disrupting chemicals, including steroids
- high molecular weight chemicals, such as polymers and proteins
- organophosphates
- allergens

Note: Excluded from TTC concept for cosmetic ingredients (according to current opinion of SCHER, SCCP, SCENIHR, 2008)

- all as cited in Kroes et al. (2004) – see above – and:
- aflatoxins, N-nitrosamines, azoxy-compounds, heterocyclic amines
- particulate matters, including nanomaterials
- genotoxic and/or carcinogenic compounds
- compounds with local (skin) effects, e.g. sensitisation / irritation
- compounds with potential pharmacological activity

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