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Identification of the substances from the Carcinogenic Potency Database (CPDB) which are of particular concern even if ingested at doses below 0.0025 µg/kg body weight per day

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)

Abstract

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) was asked by the European Commission to supply information to supplement the EFSA 2015 opinion on high-density polyethylene (HDPE) recycling processes in a step-wise manner. The Terms of Reference required to supply a list of substances for which the most severe exposure threshold is applicable and to consider Table 1 column 1 in the 2004 study by Kroes et al. which lists categories of substances for which this threshold is not applicable. The CEF Panel concludes that it is not possible to provide an exhaustive list of substances 'for which the most severe exposure threshold is applicable' as such a list would have to be established based on all known substances, excepting a comparatively small number of substances excluded by the criteria in the approach taken. The CEF Panel has analysed the most recent Carcinogenic Potency Database consisting of 1,547 substances, and identified and listed those substances which are of particular concern even if ingested at, or below an intake level of 0.0025 µg/kg body weight per day, following the approach taken by the 2004 study by Kroes et al. The CEF Panel emphasises that this opinion does not impact the risk assessment approach taken in the opinion, adopted in February 2015, on processes producing recycled HDPE for use as a food contact material, or its conclusions.

Keywords: Carcinogenic potency, exposure threshold, TD_{50}

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Correspondence: fip@efsa.europa.eu

Panel members: Claudia Bolognesi, Laurence Castle, Jean-Pierre Cravedi, Karl-Heinz Engel, Paul Fowler, Roland Franz, Konrad Grob, Rainer Gürtler, Trine Husøy, Sirpa Kärenlampi, Wim Mennes, Maria Rosaria Milana, André Penninks, Vittorio Silano, Andrew Smith, Maria de Fátima Tavares Poças, Christina Tlustos, Detlef Wölfle, Holger Zorn and Corina-Aurelia Zugravu.

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

The European Food Safety Authority (EFSA) received two applications[1] on processes producing recycled high-density polyethylene (HDPE) for use as a food contact material under Regulation (EC) No 282/2008. The processes are used to recycle post-consumer HDPE bottles which have been in contact with food, mainly milk, to produce recycled HDPE pellets. To this end post-consumer HDPE bottles are collected from mixed household waste. According to Article 3 (c) (ii) of Regulation (EC) No 282/2008 it needs to be demonstrated, by means of a challenge test or other appropriate scientific evidence, that recycling processes can reduce contamination of the plastic input to a concentration that does not pose a risk to human health. In its opinion published on 18 February 2015[2] EFSA states that the information supplied by the applicants did not allow to conclude on the safety of these processes. In particular, data on the contamination of mixed household (post-consumer) waste were not presented. The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) accordingly emphasises in its conclusion that: '...the uncertainties arising from the lack of sufficient scientific knowledge and the consequent conservatism of the selected criteria could allow the conclusion that a process is safe when criteria are met but do not allow a conclusion to be reached on the safety of the processes when the criteria are not met.'

EFSA therefore considered a worst case scenario, i.e. presence of substances with structural alerts raising concern for potential genotoxicity. Under this assumption potential migration from the recycled material should result in a dietary exposure below 0.0025 µg/kg body weight/day. Under Article 6 of Regulation (EC) No 282/2008 the decision granting the authorisation may, amongst others, include conditions or restrictions of the recycling process.

Moreover the Commission may take into account other legitimate factors relevant to the matter under consideration. To this end the Commission would need to establish whether the 'Biffa Polymers' and 'CLRrHDPE' recycling processes could meet EFSA's criteria under the assumption that certain groups of contaminants are not present in the source waste stream. Respective groups of substances have been identified e.g. in EFSA's Scientific Opinion on Exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC).[3]

Here the following substance classes are distinguished and associated with dietary exposure thresholds:

1) substances with a structural alert for genotoxicity
2) organophosphate and carbamate substances with anti-cholinesterase activity
3) Cramer Class III and Cramer Class II substances
4) Cramer Class I substances

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the Commission asks the European Food Safety Authority to provide an opinion supplementing its opinion ON-4016 with the following information:

- additional exposure threshold values that would be applicable if certain categories of contaminants would not be present in specific types of household waste streams;
- an assessment on the basis of these additional exposure threshold values of whether each of the two processes would be capable of meeting EFSA's criterion for the recycling of post-consumer HDPE bottles into pellets to manufacture bottles for milks and fruit juices;
- an assessment of the maximum allowable trace amounts in household waste of substances which would be covered under the most severe exposure threshold value (i.e. the value used

[1] See EFSA-Q-2009-00961 and EFSA-Q-2010-00020
[2] http://www.efsa.europa.eu/en/efsajournal/doc/4016.pdf
[3] EFSA Journal 2012;10(7):2750, 103 pp. Available online: http://www.efsa.europa.eu/en/efsajournal/pub/2750.htm

in the published opinion) for the process of meeting the present criteria, taking into account the established sorting and cleaning efficiency;

- a list of substances known to EFSA to which this most severe exposure threshold value is applicable;
- a concise literature review of papers that discuss possible constituents of household waste, such as the attached supporting document, including a categorisation of the substances mentioned in these papers (see table 1 of the supporting document) into three categories on the basis of scientific information already known to EFSA: substances to which this most severe exposure threshold value would be applicable, substances would be included in one of the other categories and substances on which EFSA does not have sufficient scientific information to determine this.
- an assessment which surrogate substance used by the applicants in the challenge tests reported in the opinion would be most representative for each potential contaminant identified in the two bullets above.

Upon EFSA's request, the European Commission (EC) clarified the Terms of Reference in a letter sent to EFSA on 23 June 2015 which is reported below.

> 'To act in an efficient manner we agreed on a step-by-step approach. Hence you would attempt to identify the substances for which the most severe exposure threshold value (i.e. 0.15 µg/person/day) is applicable and provide the list of these substances. To this end we ask you to consider the approximately 86 substances referred to in the publication of Kroes et al. (2004) Table 1, column 1 (i.e. under 0.15 µg) on the basis of the Carcinogenic Potency Database (CPDB). We would be grateful for a swift indication as to when you will be able to provide the list of substances'.

1.2. Interpretation of the Terms of Reference

In the context of the European Commission's background information and request to supplement the opinion on processes producing recycled HDPE for use as a food contact material, this opinion addresses the first part of the step-wise approach requested in the European Commission letter of 23 June 2015. This letter required to supply a list of substances for which the most severe exposure threshold is applicable, and to consider Table 1, column 1 in the 2004 study by Kroes et al. which lists categories of substances for which this threshold is not applicable.

Referring implicitly to the EFSA's Scientific Opinion on Exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC; EFSA SC, 2012), the European Commission asks EFSA 'to identify the substances for which the most severe exposure threshold value (i.e. 0.15 µg/person per day) is applicable, and provide the list of these substances'. As specified in that opinion, the TTC approach is applicable to all substances for which the chemical structure is known, but for which there are few or no relevant toxicity data, provided that these substances are not part of one of the exclusion categories given in that opinion or that legislation does not require the submission of data. This being so, the list requested here would be essentially endless as it would have to be established based on all substances[4], excepting the comparatively small number excluded from the approach or those substances for which toxicity data exist. Therefore, such a list cannot be compiled and was not provided to address this question.

The present opinion therefore specifically addresses only the second task outlined in the European Commission's letter of 23 June 2015, i.e. considering high potency carcinogens as referred to in Table 1, column 1 in the article of Kroes et al. (2004) in relation to the current CPDB. According to the Kroes et al. (2004) publication, the 86 substances referred to in Table 1, column 1, are substances for which the cancer risk was estimated to be greater than one in a million (10^{-6}) at an intake level of 0.15 µg/person per day (calculated for a 60-kg person and an intake of 3 kg of diet per day).

[4] Namely, substances for which the chemical structure is known, but for which there are few or no relevant toxicity data, provided these substances are not part of one of the exclusion categories or that legislation does not require the submission of data (please consult EFSA SC, 2012).

For the purpose of this opinion, the CEF Panel has applied the same linear extrapolation approach[5] of Kroes et al. (2004) to identify and list those substances which, on the basis of the CPDB, are of particular concern even if ingested at doses at or below 0.0025 µg/kg body weight (bw) per day. The current CPDB (version of September 2011) consists of more than double the number of substances that were used to identify the threshold value mentioned by the European Commission and that is why for this opinion the current CPDB was used. The EFSA Scientific Committee (SC) recommended to express the value of 0.15 µg/person per day on a body weight basis and this corresponds to 0.0025 µg/kg bw per day.

2. Data and Methodologies

2.1. Data

The Terms of Reference specifically mentions 86 substances reported in Table 1, column 1, of Kroes et al. (2004). The aim of the Kroes et al. table was to identify the structural alerts that would give the highest calculated risks if present in the diet at different intake levels, based on the CPDB (Gold and Zeiger, 1997). In that study, column 1 of Table 1 reports the number and fraction of various structural groups in the database that would give estimated cancer risks greater than 1×10^{-6} even at an intake level of 0.15 µg/person per day (calculated for a 60-kg person and an intake of 3 kg of diet per day). As Kroes et al. (2004) did not list the identity of these 86 substances and since the database has meanwhile been updated and substantially expanded, the CEF Panel has used the current CPDB database (version of September 2011, available online: http://toxnet.nlm.nih.gov/cpdb/, last accessed on 28 January 2016) which contains 1,547 substances, to address the European Commission's request.

The CPDB contains detailed data in an electronic format including verified chemical specifications (e.g. chemical name, Chemical Abstracts Service (CAS) registry number, chemical and structural information), and TD_{50} values for the substances listed. The TD_{50} is defined as follows: for a given target site(s), the TD_{50} is that chronic dose-rate in mg/kg bw per day which, if administered chronically for the standard lifespan of the species, will halve the probability of remaining tumour-free throughout that period.

2.2. Methodologies

The database contains 1,547 substances for which TD_{50} values are available.

To address the Terms of Reference, the following steps were taken:

- The lowest oral TD_{50} for each substance was selected, to ensure the most conservative decision on the potency of a substance by the oral route (i.e. excluding intraperitoneal and intravenous TDs_{50}).
- The records with effect sites labelled as 'all tumour bearing animals' (i.e. chemicals for which the only positive results in the CPDB were for 'all tumour bearing animals', and there was no target site reported) were excluded.
- Mixtures and substances for which the CAS number was not reported were also excluded.
- Only chronic studies were included.
- The substances with a TD_{50} at or below 1.25 mg/kg bw per day were extracted from the database. This cut off value was derived by back calculation from the value indicated by the European Commission (0.0025 µg/kg bw per day) by linear extrapolation to the respective TD_{50}. This is using the same approach as that taken by Kroes et al. (2004) when extrapolating from a TD_{50} to a life time cancer risk of 1 in a million[5].
- The final list of the substances with a TD_{50} at or below 1.25 mg/kg bw per day was obtained and is shown in Table 1 of this opinion.

[5] The CEF Panel is aware and agrees with the reservations expressed by the EFSA Scientific Committee (EFSA, 2005) regarding extrapolating – by mathematical modelling – from carcinogenicity data in experimental animals observed at high doses to estimate risks to humans at orders of magnitude lower exposures from substances that are both genotoxic and carcinogenic.

3. Assessment

By using the same approach taken in the study by Kroes et al. (2004), the CEF Panel identified 143 substances from the updated CPDB (including overall 1,547 substances) which are of particular concern even if ingested at doses at or below 0.0025 µg/kg bw per day (see the list in Table 1, Appendix A). The large majority of the listed substances belong to the exclusion categories for which the TTC approach would not be used (e.g. high potency carcinogens, substances predicted to bioaccumulate, metal compounds, steroids) (EFSA SC, 2012). The structural features of the listed substances include aflatoxin-like, azoxy, benzidine, biphenyl, hydrazine and nitroso moieties.

This opinion is based on the CPDB and is restricted to that database only. Therefore, the provided list of substances is limited and should not be considered as an exhaustive list.

The TTC approach is applicable to all substances for which the chemical structure is known, but for which there are few or no relevant toxicity data, provided these substances are not part of one of the exclusion categories given in the EFSA SC opinion (EFSA SC, 2012) or that legislation does not require the submission of data. This being so, the list requested in the first part of the Terms of Reference would be essentially endless because it would have to be established based on all substances[6], excepting the comparatively small number excluded from the approach or those substances for which toxicity data exist. The most severe exposure threshold value of 0.0025 µg/kg bw per day would be applicable to all of the other substances in such a list. In case the weight of evidence indicates no concern of the substance being a DNA-reactive carcinogen, a higher exposure threshold could be considered.

4. Conclusions

The CEF Panel has analysed the most recent CPDB consisting of 1,547 substances and identified those substances of particular concern even if ingested at doses at or below 0.0025 µg/kg bw per day, following the approach taken by Kroes et al. (2004). These substances are listed in Table 1 in Appendix A.

The CEF Panel concludes that it is not possible to provide an exhaustive list of substances 'for which the most severe exposure threshold is applicable'.

The CEF Panel emphasises that this opinion does not impact the risk assessment approach taken in the opinion on processes producing recycled HDPE for use as a food contact material or its conclusions.

References

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[6] Namely, substances for which the chemical structure is known, but for which there are few or no relevant toxicity data, provided these substances are not part of one of the exclusion categories and legislation does not require the submission of data (please consult EFSA SC, 2012).

Abbreviations

bw	body weight
CAS	Chemical Abstracts Service
CEF Panel	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CPDB	Carcinogenic Potency Database
HDPE	high-density polyethylene
SC	EFSA Scientific Committee
TD_{50}	chronic dose-rate in mg/kg bw per day which, if administered chronically for the standard lifespan of the species, will halve the probability of remaining tumour-free throughout that period.
TTC	threshold of toxicological concern

Appendix A – Table 1

Table 1: Substances from the Carcinogenic Potency Database which are of particular concern even if ingested at doses at or below 0.0025 µg/kg body weight per day

Name as listed in the CPDB	CAS	Oral TD_{50} minimum (mg/kg bw per day)[(a)]	Rodent species
4-Acetylaminobiphenyl	4075-79-0	1.18	Rat
2-Acetylaminofluorene	53-96-3	1.22m	Rat
Aflatoxicol	29611-03-8	0.00247	Rat
Aflatoxin B1	1162-65-8	0.0032m,P,v	Rat
Aflatoxin, crude	1402-68-2	0.00299m	Rat
1-Allyl-1-nitrosourea	760-56-5	0.341m	Rat
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	712-68-5	0.662	Rat
4-Aminodiphenyl.HCl	2113-61-3	0.98	Rat
1-Amyl-1-nitrosourea	10589-74-9	0.555m	Rat
Aristolochic acid, sodium salt (77% AA I, 21% AA II)	10190-99-5	0.0141m	Rat
Azoxymethane	25843-45-2	0.0466m	Rat
1-Azoxypropane	17697-55-1	0.000241P	Rat
Benzo(a)pyrene	50-32-8	0.956	Rat
Bis-(chloromethyl)ether	542-88-1	0.00357	Rat
Budesonide	51333-22-3	0.291	Rat
N-Butyl-*N*-(4-hydroxybutyl) nitrosamine	3817-11-6	0.457m,P,v	Rat
N-n-Butyl-*N*-nitrosourea	869-01-2	0.517m,v	Rat
Cadmium chloride	10108-64-2	0.0136m,v	Rat
Cadmium sulfate (1:1)	10124-36-4	0.0217m	Rat
Chlorambucil	305-03-3	0.896m	Rat
3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone	77439-76-0	0.583m	Rat
Clivorine	33979-15-6	0.5	Rat
Cobalt sulfate heptahydrate	10026-24-1	0.137m	Rat
Dacarbazine	4342-03-4	0.71	Rat
1,2-Dibromo-3-chloropropane	96-12-8	0.259m	Rat
1,4-Dichlorobutene-2 (65% trans-, 35% cis-)	764-41-0	0.297m	Rat
Dieldrin	60-57-1	0.912m,P	Mouse
Diethylstilbestrol	56-53-1	0.223m,v	Mouse
2,5-Dimethoxy-4´-aminostilbene	5803-51-0	0.721	Rat
3,3´-Dimethoxybenzidine.2HCl	20325-40-0	1.04m	Rat
5,6-Dimethoxysterigmatocystin	65176-75-2	<0.364P	Rat
Dimethylaminoethylnitrosoethylurea, nitrite salt	142713-78-8	0.704	Rat
7,12-Dimethylbenz(a)anthracene	57-97-6	0.084	Mouse
3,3´-Dimethylbenzidine.2HCl	612-82-8	0.629m	Rat
Dimethylcarbamyl chloride	79-44-7	0.625	Hamster
1,2-Dimethylhydrazine.2HCl	306-37-6	0.114m,P	Mouse
2-(2,2-Dimethylhydrazino)-4-(5-nitro-2-furyl)thiazole	26049-69-4	0.41P	Rat
Dimethylnitramine	4164-28-7	0.547m,v	Rat
Dinitrosocaffeidine	145438-97-7	0.183	Rat
Dinitrosohomopiperazine	55557-00-1	0.0615m	Rat
2,6-Dinitrotoluene	606-20-2	0.292m	Rat
a-Ecdysone	3604-87-3	0.0358m	Mouse
Enovid	8015-30-3	0.279m,v	Mouse
Ethinyl estradiol	57-63-6	0.2	Rat
Z-Ethyl-*O*,*N*,*N*-azoxyethane	16301-26-1	0.022	Rat
Z-Ethyl-*O*,*N*,*N*-azoxymethane	57497-29-7	0.0189	Rat
1-Ethyl-1-nitrosourea	759-73-9	0.948m	Rat
Ethylene imine	151-56-4	0.377m,P	Mouse
1-Ethylnitroso-3-(2-hydroxyethyl)-urea	96724-44-6	0.522m	Rat
1-Ethylnitroso-3-(2-oxopropyl)-urea	110559-84-7	0.181m,P	Rat
4´-Fluoro-4-aminodiphenyl	324-93-6	1.14m	Mouse
N-4-(4´-Fluorobiphenyl)acetamide	398-32-3	1.01	Rat
2-Fluoroethyl-nitrosourea	69112-98-7	0.125	Rat

Name as listed in the CPDB	CAS	Oral TD_{50} minimum (mg/kg bw per day)[(a)]	Rodent species
Furan	110-00-9	0.396m	Rat
Heptachlor	76-44-8	1.21m	Mouse
Hexamethylphosphoramide	680-31-9	0.0344m	Rat
N-Hexylnitrosourea	18774-85-1	0.513m,P	Rat
Hydrazine	302-01-2	0.613m,v	Rat
2-Hydrazino-4-(*p*-aminophenyl) thiazole	26049-71-8	1.03	Rat
N-Hydroxy-2-acetylaminofluorene	53-95-2	0.988m	Rat
1-(2-Hydroxyethyl)-nitroso-3-ethylurea	96724-45-7	0.562m	Rat
1-(2-Hydroxyethyl)-1-nitrosourea	13743-07-2	0.244m,v	Rat
2-Hydroxyethylhydrazine	109-84-2	0.397m	Mouse
1-(3-Hydroxypropyl)-1-nitrosourea	71752-70-0	0.978m	Rat
Indomethacin	53-86-1	1.15	Rat
IQ	76180-96-6	0.812m,v	Rat
Isatidine	15503-86-3	0.716m	Rat
Kepone	143-50-0	0.982m	Mouse
Lasiocarpine	303-34-4	0.389m	Rat
Methimazole	60-56-0	1.14m	Rat
N-Methyl-N´-nitro-*N*-nitrosoguanidine	70-25-7	0.803m,v	Rat
4-(4-*N*-Methyl-*N*-nitrosaminostyryl)quinoline	16699-10-8	0.699m	Rat
3-Methylcholanthrene	56-49-5	0.491m,P	Rat
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol	76014-81-8	0.103	Rat
4-(Methylnitrosamino)-1-(3-pyridyl)-1-(butanone)	64091-91-4	0.0999m	Rat
Methylnitrosocyanamide	33868-17-6	0.48	Rat
Monocrotaline	315-22-0	0.94m	Rat
3-Nitro-3-hexene	4812-22-0	0.346	Mouse
2-Nitrofluorene	607-57-8	0.285	Rat
Nitroso-Baygon	38777-13-8	0.364	Rat
Nitroso-2-oxopropylethanolamine	92177-49-6	0.997	Hamster
N-Nitroso-bis-(4,4,4-trifluoro-*N*-butyl)amine	83335-32-4	0.748m	Rat
1-Nitroso-5,6-dihydrouracil	16813-36-8	0.0983m	Rat
N-Nitroso-2,3-dihydroxypropyl-2-hydroxypropylamine	89911-79-5	0.0535	Rat
Nitroso-2,3-dihydroxypropyl-2-oxopropylamine	92177-50-9	0.0352	Rat
Nitroso-5-methyloxazolidone	79624-33-2	0.172	Hamster
1-Nitroso-1-hydroxyethyl-3-chloroethylurea	96806-34-7	0.356m	Rat
N-Nitroso-1,3-oxazolidine	39884-52-1	0.798m	Hamster
1-Nitroso-1-(2-hydroxypropyl)-3-chloroethylurea	96806-35-8	0.873m	Rat
N-Nitroso-(2-hydroxypropyl)-(2-hydroxyethyl)amine	75896-33-2	1.02	Rat
(a): *N*-Nitroso-*N*-methyl-*N*-dodecylamine	55090-44-3	0.537m,P	Rat
N-Nitroso-*N*-methyl-4-fluoroaniline	937-25-7	0.255	Rat
N-Nitroso-*N*-methylurethan	615-53-2	0.127	Hamster
Nitroso-*N*-methyl-*N*-(2-phenyl) ethylamine	13256-11-6	0.00998m	Rat
N-Nitroso-*N*-methylurea	684-93-5	0.0927	Rat
3-Nitroso-2-oxazolidinone	38347-74-9	0.385m,P	Rat
Nitroso-1,2,3,6-tetrahydropyridine	55556-92-8	0.0601m,P	Rat
1-Nitroso-3,4,5-trimethylpiperazine	75881-18-4	0.151	Rat
N-Nitrosoallyl-2,3-dihydroxypropylamine	88208-16-6	0.825	Rat
N-Nitrosoallyl-2-hydroxypropylamine	91308-70-2	0.877	Rat
N-Nitrosoallyl-2-oxopropylamine	91308-71-3	0.335	Rat
N-Nitrosoallylethanolamine	91308-69-9	0.491	Rat
Nitrosoamylurethan	64005-62-5	1.01	Rat
N-Nitrosobenzthiazuron	51542-33-7	1.13	Rat
N-Nitrosobis(2-hydroxypropyl) amine	53609-64-6	0.846m	Rat
N-Nitrosobis(2-oxopropyl)amine	60599-38-4	0.491m	Rat
Nitrosodibutylamine	924-16-3	0.691	Rat
N-Nitrosodiethylamine	55-18-5	0.0265m,v	Rat
N-Nitrosodimethylamine	62-75-9	0.0959m,v	Rat
N-Nitrosodipropylamine	621-64-7	0.186	Rat
Nitrosoethylmethylamine	10595-95-6	0.0503	Rat

Name as listed in the CPDB	CAS	Oral TD_{50} minimum (mg/kg bw per day)[(a)]	Rodent species
Nitrosoethylurethan	614-95-9	0.0904m	Rat
Nitrosoheptamethyleneimine	20917-49-1	0.0378m	Rat
N-Nitrosohexamethyleneimine	932-83-2	0.528m	Mouse
Nitrosomethyl-3-carboxypropylamine	61445-55-4	0.982	Rat
N-Nitrosomethyl-2,3-dihydroxypropylamine	86451-37-8	0.646	Rat
N-Nitrosomethyl-2-hydroxypropylamine	75411-83-5	0.0463m	Rat
N-Nitrosomethyl(2-oxopropyl) amine	55984-51-5	0.0172m	Rat
2-Nitrosomethylaminopyridine	16219-98-0	0.214	Rat
Nitrosomethylaniline	614-00-6	0.142m,P,v	Rat
N-Nitrosomorpholine	59-89-2	0.109m	Rat
N′-Nitrosonornicotine	53759-22-1	0.0957	Rat
N′-Nitrosonornicotine-1-N-oxide	78246-24-9	0.876m	Rat
N-Nitrosopyrrolidine	930-55-2	0.679	Mouse
N-Nitrosothialdine	81795-07-5	0.483	Rat
Ochratoxin A	303-47-9	0.136m	Rat
1-(2-Oxopropyl)nitroso-3-(2-chloroethyl)urea	110559-85-8	0.338m	Hamster
2-Oxopropylnitrosourea	89837-93-4	0.13m	Hamster
Petasitenine	60102-37-6	0.922m	Rat
Phenesterin	3546-10-9	0.523	Rat
Polybrominated biphenyl mixture	67774-32-7	0.322m	Rat
b-Propiolactone	57-57-8	1.24m	Mouse
Reserpine	50-55-5	0.306	Rat
Retrorsine	480-54-6	0.862	Rat
Riddelliine	23246-96-0	0.119m	Rat
Sterigmatocystin	10048-13-2	0.152m,v	Rat
Strobane	8001-50-1	0.884m	Mouse
T-2 toxin	21259-20-1	0.883	Mouse
2,3,7,8-Tetrachlorodibenzo-p-dioxin	1746-01-6	0.0000235m,v	Rat
Tetranitromethane	509-14-8	0.447m	Rat
Triamcinolone acetonide	76-25-5	0.053	Rat
1,2,3-Trichloropropane	96-18-4	0.875m	Mouse
Trp-*P*-1 acetate	75104-43-7	0.575m	Rat

Source: CPDB, updated September 2011 (http://toxnet.nlm.nih.gov/cpdb/), last accessed on 28 January 2016.
The letters following the oral TD_{50} value present in the original database have the following meaning:
m: There is more than one positive experiment in the species, and TD_{50} values from each positive experiment are used in the calculation of the reported Harmonic mean of TD_{50};
v: Variation is greater than ten-fold among statistically significant (two-tailed $p < 0.1$) TD_{50} values from different positive experiments;
P: The harmonic mean of TD_{50} for the species includes a value for the upper 99% confidence limit on TD_{50} from an experiment with a target site with 100% tumour incidence in dosed animals. No TD_{50} could be calculated for the site because only summary incidence data (not life table) were available.