Evaluation of time extrapolation factors based on the database RepDose

M. Batke[a], S. Escher[a], S. Hoffmann-Doerr[b], C. Melber[a], H. Messinger[b], I. Mangelsdorf[a]

[a]Fraunhofer ITEM, Nikolai-Fuchs-Str. 1, 30625 Hannover, Germany
[b]Cognis GmbH, Henkelstraße 67, 40589 Düsseldorf, Germany

Address for manuscript correspondence:
Dr. Monika Batke, Fraunhofer-Gesellschaft
Institut für Toxikologie und experimentelle Medizin, Abteilung Chemikalienbewertung
Nikolai-Fuchs-Str. 1, 30625 Hannover, Germany
Telefon: +49/(0)511 5350 344
Fax: +49/(0)511-5350 335
mailto:monika.batke@item.fraunhofer.de

Abstract

In chemical risk assessment for many substances only short-term animal studies are available for the evaluation of long-term human exposure. Therefore usually extrapolation factors (EF) are used to extrapolate NOAELs from existing short-term studies to NOAELs for long term exposure. In this report time EFs are derived, based on NOEL/C or LOEL/C ratios (short term N(L)OEL/ long term N(L)OEL) from the large datasets of the database RepDose (www.fraunhofer-repdose.de) on repeated dose toxicity for oral or inhalation administration. Within a tiered approach several sources of variability e.g. use of LOEL/C ratios or differences in dose spacing were analyzed and if needed subsequently excluded. The reduction of data variability resulted in "final" EFs datasets, which are as far as possible based on compound-specific, time-dependent differences in toxicity. For distribution functions of oral repeated dose toxicity studies characterised by GM, GSD and 90^{th} percentiles the following data are obtained: subacute-to-subchronic – GM 1.3, GSD 2.4 , 90^{th} 4.0, subacute-to-chronic – GM 3.4, GSD 3.7 , 90^{th} 18.2, and subchronic-to-chronic – GM 1.4, GSD 2.1, 90^{th} 3.6. The number of data for inhalation exposure is limited, but with regard to systemic toxicity the derived EFs confirm the respective oral EFs.

Keywords

time extrapolation, subacute, subchronic, chronic, RepDose, risk assessment, safety factors

1. Introduction

A sound risk assessment will ideally use long-term animal studies to assess the risk of a given substance for a long-term human exposure situation. Long-term animal studies, however, are expensive and need a considerable number of animals: Therefore for many substances only short-term studies with subacute to subchronic exposure durations are available. A major aim of the present European legislation is to minimize animal testing. Thus, instead of performing new long term studies, existing short term studies are used for risk assessment.

In various regulatory arenas several assessment factors are in use to extrapolate from short-term studies to chronic or lifetime NOAELs. In fact numerous studies have investigated time EFs, and there is still no consensus about which general time EFs are most appropriate for human risk assessment and whether specific factors can be applied to a predefined category of substances.

In the second half of the 20th century the use of extrapolation factors (EFs) for studies shorter than lifetime have been evaluated and discussed for different applications (e.g. Weil 1972, Dourson and Stara 1983, Calabrese and Gilbert, 1993). It was concluded that chronic studies often lead to lower NOAELs due to various reasons such as bioaccumulation of the substance, latency before damage, altered toxicodynamics/toxicokinetics in aging animals and increased statistical power due to the larger number of animals and EFs were proposed to reflect these differences.

To derive time EFs the ratio of the NOAELs from a short- and a long-term study with the same chemical is calculated. By analyzing these ratios for a large number of chemicals it is possible to calculate a general or "default" time EF that can be applied to the NOAEL from a short-term study to estimate the NOAEL for a long-term study. Thus, according to Calabrese and Gilbert (1993), a chronic NOAEL can be estimated based on limited datasets containing only short-term studies.

In the following years several studies have been published that analyzed the distribution of NOAEL ratios of short-term and long-term studies. The comprehensive analyzes and reports of Vermeire et al. (1999 and 2001), Kalberlah and Schneider (1998) and Kalberlah et al. (2002) have to be mentioned here. Their distributions are log-normally distributed and have been characterized by GMs, geometric standard deviations (GSD) and the 90th and/or 95th percentiles. They, however, are based on limited numbers of chemicals and studies and result in widespread distributions as several possible sources of data variability are included. In this report we used a larger dataset derived from the database RepDose (Bitsch et al 2006). Although studies with different durations exist for a chemical in this database, they may have been performed with different species, strains, scopes of examinations and dose spacing. In a tiered approach the influences of different parameters (e.g. study quality, dose spacing) on the distribution of the EF were analyzed and sources of data variability which were identified, were excluded stepwise. The aim was to derive final datasets with a minimum of variability mainly due to the true chemical variability and the use of NOEL ratios. Datasets for oral and inhalation exposure for subacute-to-subchronic, subacute-to-chronic, and subchronic-to-chronic extrapolation were analyzed and discussed.

2. Material and Methods

2.1 Selection of studies

Several sources of study data were used to compile a large database applicable to the analyzis of time EFs. The RepDose database (www.fraunhofer-repdose.de, Bitsch el al. 2006), initially funded by CEFIC LRI, was used for the analyzis of EFs. RepDose is a database on repeated-dose toxicity studies on industrial chemicals in rodents with oral and inhalation exposure. Peer-reviewed studies from criteria documents such as MAK documentations, EHC, CICADs, EU risk assessments, OECD SIDS, BUA reports, Reports of the German BG Chemie as well as NTP studies were used for RepDose entries. Further, some studies provided by Cesio (Comité Europeen des Agents de Surface et de leurs Intermédiaires Organiques) were added to RepDose, including some confidential studies. Further studies of the ToxBase database (TNO Netherlands Organisation for Applied Scientific Research Building and Construction Research) which focus on pesticides were included into RepDose. The information about study design, affected organs, observed effects, NOEL/Cs as well as LOEL/Cs was extracted and entered into RepDose. An internal score was used to classify study quality: studies conforming to guidelines which correspond to Klimisch code 1, and studies with minor deficiencies which correspond to Klimisch code 2. The combined databases contain about 650 substances being characterized in about 2200 studies with subacute to chronic study durations.

For each study a N(L)OEL(C) (no (lowest) observed effect level (concentration)) value is given. The N(L)OAEL(C)s (no (lowest) observed adverse effect level (concentration)) value is not recorded, as expert judgement is needed to decide on the adversity of the observed effect. Expert judgement depends on the background and experience of the scientist and thus impedes consistent study documentation. Furthermore, the use of N(L)OEL(C)s allows a full documentation of all observed target organs and effects. NOEL and LOEL values were analyzed in mmol/kg bw/d for oral exposure and NOECs and LOECs in ppm for inhalation exposure. In general EFs were calculated as ratios of the studies' NOEL/Cs or, if not available, the studies' LOEL/Cs. NOEL/C versus LOEL/C ratios were not included. The application of a consistent expert judgement in the review for the final level dataset leads to the derivation of NOAEL ratios in the final level dataset. General settings for the chemical-specific comparison of the rodent studies were selection of the same species, and the same route of administration , e.g. feed-feed or gavage-gavage. Study durations included in the analyzes were 20 to 33 days for subacute studies, 83 to 99 days for subchronic, and more than 699 days for chronic studies. The references of all study pairs included in the analyzis are given in the supplementary material.

2.2 Tiered approach

In a tiered approach EFs were analyzed at:

1. Study level: EFs based on all appropriate study pairs were analyzed. The number of EFs per substance depends on the number of appropriate study pairs for this substance.

2. Chemical level: The median EF was taken for substances having more than one EF at the study level.
3. Analyzis of parameters influencing the EFs and their distribution functions: Despite time-dependent differences in toxicity induced by chemical properties also other parameters such as difference in study design may influence the EFs and their distribution functions. The influences of the following parameters were analyzed: dose spacing, data quality, general comparability, and the replacement of LOAEL ratios with target organ EFs (EF_{TO}).
4. Final level: The results obtained in step 1 to 3 were used to compile the "final level". Pairs of comparable studies with regard to study design were selected taking into account the evaluated sources of non-chemical induced data variability. Based on the consistent evaluation of the studies according to the previous steps the EFs in the final level are based on NOAEL ratios rather than NOEL ratios.

Steps 3 and 4 of the tiered approach are explained more detailed in the following sections.

2.3 Analyzis of parameters influencing EFs and their distribution functions

In the largest dataset subchronic to chronic oral exposure the influence of differences in study parameters such as dose spacing, data quality, general comparability was analyzed. Further, the replacement of LOAEL ratios with EF_{TO} was evaluated.

2.3.1 Dose spacing differences

Oral subchronic and chronic studies which derive NOEL and LOEL values were selected. The dose spacing ($DS_{study\ type}$) in each study was calculated as LOEL divided by NOEL. For each study pair the DS of the subchronic study was divided by the dose spacing of the chronic study ($DS_{ratio} = DS_{subchr}/DS_{chr}$). Three categories of dose spacing differences were discriminated: study pairs with similar dose spacing (DS ratio between 0.5 and 2), study pairs with different dose spacing and DS ratio ≤ 0.5 ($DS_{ratio \leq 0.5}$) and study pairs with different dose spacing and DS ratio ≥ 2 ($DS_{ratio \geq 2}$).

2.3.2 Data quality

On the study level, studies were split into one dataset comprising only guideline or close to guideline studies (Klimisch code 1) and a second dataset comprising only studies with minor deficiencies (Klimisch code 2). EFs based on "mixed study quality" ratios (Klimisch code 1 and 2 studies) were not included in this analyzis. The resulting EF distributions of both dataset were compared to each other.

2.3.3 General study comparability

The studies in the oral subchronic-to-chronic extrapolation dataset were reviewed for their comparability as explained in the following. EF_{NOAEL} ratios were selected for pair of studies with a similar scope of examination, similar dose spacing, and ideally but not necessarily conducted with same strain and/or by the same laboratory/author. NOEL values triggered by well-known adaptive or age-related effects, such as haemosiderosis or α2u-globulin nephropathy in rats (Mohr et al. 1992),

were excluded from this dataset. In some cases, where the NOAEL value of the shorter (subchronic) study duration was missing, an EF was calculated using the pair of study LOAELs. In this case the resulting EF_{LOAEL} is a conservative estimate for the following reason: if the subchronic study would have tested lower doses the true $LOAEL_{subchr}$ might decrease, whereas the $LOAEL_{chr}$ remains stable as it is confirmed by its $NOAEL_{chr}$ value. Thus, the resulting EF_{LOAEL} represents a maximum value for this pair of studies (EF_{max}). The EF distribution functions of these comparable studies and the median values for the same chemicals from the chemical level were compared.

2.3.4 Replacement of LOAEL ratios with EFs_{TO}

Numerous comparable studies, as defined in section 2.3.3., were identified that do not derive NOAEL values. This dataset was used to evaluate the influence of LOAEL ratios. It was evaluated whether EFs_{LOAEL} can be replaced by EFs_{TO}. In addition to the criteria defined in section 2.3.3 the studies of both durations need to have a most sensitive common target organ, affected above but not at the study LOEL, thus having an organ-specific NOAEL and LOAEL. This idea is based on the observation that all study pairs with a NOEL and a LOEL value in both durations in subchronic-to-chronic study level show in 46 (83%) out of 59 EFs at least one common target organ. The corresponding organ NOAELs were used to calculate the EF_{TO}. Further the sensitive common target organ needed to have a comparable, time-dependent effect in both study durations. Target organs with effects such as adaptive, local or non-dose dependent effects as well as effects correlated to an increased mortality at LOAEL were not included in the analyzis. Also tumours occurring only in the chronic studies with different time dependencies from neoplastic alterations in shorter durations were not used to define target organ NOAEL values. The distribution of the resulting EFs_{TO} was compared with the chemical level EFs for the same chemicals. Additionally the distribution of EFs_{TO} was compared to the distribution of EFs based on remaining LOAEL ratios of the chemical level, thus EFs for chemicals without any pair of comparable studies.

2.4 Final level

The comparable studies were selected based on the analyzes described in section 2.3. Either $EF_{NOAEL/C}$ or if not given the EF_{TO} were selected for the final level datasets for both oral and inhalation exposure. Further, only systemic effects were considered to select pairs of comparable studies for inhalation exposure.

Also $EFs_{LOAEL/C}$ were included into the dataset instead of $EFs_{NOAEL/C}$ in two exceptional situations:

a) A high difference in dose spacing was only observed for the $EF_{NOAEL/C}$ but not the corresponding $EF_{LOAEL/C}$. Here, a similar DS was found for all doses equal or higher than the LOAEL, whereas a high difference in DS occurred between LOAEL and NOAEL, with , e.g. 10 in one and 2 in the second study (Table 4, EF_{DS}).

b) The NOAEL/C was not available for the study with the shorter duration. As described in section 2.3.3 the EF_{max} was used (Table 4, EF_{max}).

In addition EFs for two chemical categories, surfactants and pesticides, were analyzed at the final level. Surfactants were identified by their chemical structure, consisting of a non-polar moiety combined with a polar moiety , e.g. alcohol ethoxylates. The structural properties of pesticides are less clearly defined including multifunctional molecules. Thus the category pesticides included all organophosphates and those chemicals used as pesticides with a JMPR publication (Joint FAO/WHO Meeting on Pesticide Residues). The categorization is documented in the supplementary material.

2.4 Statistics

The statistical analyzes were performed using STATISTICA 8.2 and the @risk 5.5.1 from Palisade. The GM and GSD of the empirical distributions were determined and the respective 90^{th} and 95^{th} percentiles calculated. Differences between datasets were analyzed with the Mann-Whitney-Wilcoxon test for unpaired and the Wilcoxon test for paired samples. Differences in the variance of the distributions were evaluated with the F-test.

3. Results

The evaluation of time extrapolation factors and their distribution functions are based on 149 chemicals derived from the RepDose DB. EFs for oral and inhalation administration for subacute-to-subchronic, subacute-to-chronic and subchronic-to-chronic extrapolation are analyzed. The numbers of study pairs and chemicals for each dataset are given in Table 1 and 2. In the present dataset 33 chemicals have studies in all three durations with either the oral or the inhalation administration. The distribution functions of the resulting time extrapolation factors are all best described as log-normal distributions (Figure 1 and supplementary data for subchronic-to-chronic extrapolation).

3.1 Study level

At the study level for oral exposure (Table 1) datasets were larger for all three time frames than for the inhalation route (Table 2). The distributions of the derived EFs for both routes are widespread and comparable (Mann-Whitney-Wilcoxon, all $p \geq 0.5$).

3.2 Chemical level

At the chemical level the number of data points in each extrapolation dataset is reduced, as the median EFs per chemical were included. For the oral datasets the number of data points compared to study level was reduced by 25 (33%) for subacute-to-subchronic, by 16 (33%) for subacute-to-chronic and by 125 (53%) for subchronic-to-chronic extrapolation (Table 1). The distributions of the subacute-to-subchronic and the subchronic-to-chronic extrapolations were similar to the study level distributions. Within the subacute-to-chronic extrapolation dataset the GM increased compared to the study level. For the overall smaller inhalation datasets (Table 2) the number of data points at the chemical level was less reduced compared to the oral chemical level: minus 8 (26%) for the subacute-to-subchronic,

minus 3 (17%) for the subacute-to-chronic, and minus 55 (54%) for the subchronic-to-chronic dataset. All distributions of EFs for the chemical level datasets were slightly higher compared to the study level, the GSDs tended to be lower and the 90th percentiles were all close to 10.
A significant difference was not detected between the corresponding EF functions for oral and inhalation exposure, as it was already observed at the study level (Mann-Whitney-Wilcoxon, all $p \geq 0.5$).

3.3 Analyzis of parameters influencing EFs and their distribution functions
The influence of selected parameters such as differences in dose spacing or data quality on the distributions of the resulting EFs was analyzed. Furthermore, the influence of the general study comparability as well as the replacement of LOAEL ratios by EF_{TO} was evaluated (Table 3). For these analyzes the largest dataset, subchronic to chronic oral exposure, was chosen which consisted of 111 EFs at the chemical level and 236 EFs at the study level (Table 1).
3.3.1 Dose spacing differences
Within all available subchronic-to-chronic study pairs 58 study pairs with a NOEL and a LOEL in both study durations were identified. After the calculation of the DS_{ratio} three datasets were distinguished: similar DS (DS_{ratio} between 0.5 and 2), different dose spacing for $DS_{ratio\leq 0.5}$ and $DS_{ratio\geq 2}$ (Table 3). The EF distribution of $DS_{ratio\leq 0.5}$, where the DS of the subchronic study is half or even lower than that of the chronic study, is shifted to higher values compared to studies with similar DS. Vice versa the EFs decrease when the dose spacing for the subchronic study is double or higher than for the chronic study ($DS_{ratio\geq 2}$). Both datasets of EF with large differences in dose spacing, $DS_{ratio\leq 0.5}$ and $DS_{ratio\geq 2}$, are significantly different (Mann-Whitney-Wilcoxon test, $p < 0.0001$). They also differ from the dataset similar dose spacing (Mann-Whitney-Wilcoxon test, $p = 0.1$ for $DS_{ratio\leq 0.5}$; $p = 0.0005$ for $DS_{ratio\geq 2}$). It can thus be stated that large differences in dose spacing result in extreme values, either in very low or very high EFs. The present analyzes indicate that incongruent dose spacing is one reason for non-chemical related data variability of the EF distribution functions and should thus be excluded in the final level dataset.
3.3.2 Study quality
Within the subchronic-to-chronic study pairs, 67 pairs with both Klimisch code 1 and 131 with both Klimisch code 2 were identified (Table 3). Both distributions were similar (Mann-Whitney-Wilcoxon test, $p = 0.76$), possibly due to the fact that the RepDose database does not contain studies of low quality or with insufficient information corresponding to Klimisch code 3 or 4. Thus the parameter study quality was not considered to improve the selection of studies in the final dataset.
3.3.3 General study comparability
Out of 111 chemicals in the subchronic-to-chronic dataset, 39 compounds were identified having two "comparable" studies with NOAEL values, as defined in section 2.3.3. For these 39 chemicals the distribution of EFs based on the comparable studies was compared to the corresponding dataset of

median EFs (chemical level, Table 3). The selection of the comparable studies has a high influence on the derivation of EFs and their respective distribution (Wilcoxon test, p = 0.09). Therefore, comparable studies, as defined here, were used to compile the final dataset for all extrapolations.

3.3.4 Replacement of LOAEL ratios by EF_{TO}

It is likely that EF_{LOAEL} in pairs of studies without NOAEL values are dependent on the selection of dose groups and thus study design as the detected LOAELs could be close or not close to the not detected NOAEL value. Exclusion of all EFs_{LOAEL}, however, would significantly decrease the amount of data, as about 50% of the EFs are LOAEL ratios: subacute-to-subchronic N=25, subacute-to-chronic N=17, subchronic-to-chronic N=67. Therefore, we analyzed the possibility to replace the EF_{LOAEL} of comparable studies by EFs_{TO}. Within the subchronic-to-chronic dataset 19 chemicals were identified for which EF_{TO} could be derived. The remaining 45 study pairs did not meet the criteria for EF_{TO} (Table 3). The EF_{TO} were then compared to the corresponding median EF_{LOAEL} of the chemical level (pair wise for each chemical) and to remaining EF_{LOAEL} for which an EF_{TO} could not be derived. All three datasets showed similar distributions (Wilcoxon tests, p = 0.75 for corresponding chemical level; Mann-Whitney-Wilcoxon test, p=0.72 for the remaining EF_{LOEL}). The decreased GSD values for the EFs_{TO} compared to the remaining EFs_{LOEL} indicate that data variability was reduced significantly (F-Test for variances $p<0.1$). This analyzis shows that not only for EFs_{NOAEL} but also for EFs_{TO} the comparability of studies reduces non-chemical-related data variability. Based on this observation the EFs_{TO} instead of EFs_{LOAEL} were included in the final dataset for all three time extrapolations.

3.4 Final level

Based on the results obtained so far the study pairs for the final level dataset were selected based on $EFs_{NOAEL/C}$ of comparable studies. $EFs_{LOAEL/C}$ were replaced by EF_{TO} where possible. The number of decisions taken in the corresponding final datasets is provided in Table 4. One EF per chemical contributes to the final dataset (Table 5).

For the oral route the GSDs and GMs decreased, compared to the respective chemical level, only for the subchronic-to-chronic dataset the GM remained nearly stable (Tables 1 and 5). Accordingly, the 90^{th} percentiles decreased. The impact of the tiered approach on the EF distributions in the dataset oral subchronic-to-chronic is summarized and visualized in Figure 1. Within the refinement process the GM remained at about 1.5 for all three datasets, whereas the number of data points and the GSDs decreased (Tables 1 and 5). The data variability was reduced significantly comparing study level to final level and chemical level to final level (F-test, $p < 0.05$). The same trend is observed for the subacute-to-subchronic and subacute-to-chronic datasets. For the subacute-to-subchronic dataset the reduction in variability from study level to final level and chemical level to final level is also significant (F-Test, $p<0.05$) whereas for the subacute-to-chronic dataset a non significant reduction is observed most probably because of the limited number of EFs in this dataset.

For the inhalation route, in the final datasets EFs are based on systemic effects only. The overall final datasets for inhalation are smaller than for oral exposure. Only the subchronic-to-chronic dataset contains a considerable number of chemicals (N = 19) resulting in a similar GM and a slightly lower GSD and 90th percentile compared to those of the chemical level (Table 2 and 5). The final datasets for subacute-to-subchronic and subacute-to-chronic NOEC ratio distributions are too small for statistical analyzes (Table 5). In the inhalation dataset the influence of local versus systemic NOECs on the EFs has to be considered and will be discussed later.

The subchronic-to-chronic datasets for oral and inhalation exposure analyzed here do not have any substances in common. The two datasets can be combined, as all EFs were derived based on systemic toxicity (Table 5, Conclusion Oral+Inhalation dataset).

Furthermore, the distributions of EFs for two subgroups of compounds, surfactants and pesticides, were analyzed for the oral datasets at the final level (Table 5). Pesticides were selected, as they represent relatively large subsets in some datasets and are known for high toxicity. Surfactants were analyzed because they are ingredients of household and consumer products that are considered to be of relatively low toxicity.

The dataset subacute-to-chronic comprises only 14 chemicals, so that the analyzis of category-specific EFs did not lead to statistically relevant values. The results, however, are still included in Table 5 to give a full overview.

The dataset subacute-to-subchronic contains 38 EFs with 7 EF derived from studies with pesticides and 12 EFs from surfactants. The GMs and GSDs for both subgroups are not significantly different compared to the remaining dataset subacute-to-chronic either without pesticides or without surfactants (Mann-Whitney-Wilcoxon test, p=0.82 for pesticides; p=0.31 for surfactants).

The dataset for subchronic-to-chronic extrapolation consists of 58 compounds with 25 EF from pesticides and 3 EF from surfactants. The distributions of the resulting EFs for all datasets for subchronic-to-chronic extrapolation were not different (Mann-Whitney-Wilcoxon tests p=0.60 for pesticides and p=0.40 for surfactants versus the remaining other chemicals). Finally, the datasets of the two categories are limited and do not differ from the overall datasets.

4. Discussion

The overall objective of this report was the derivation of EFs depicting the chemical-induced differences over time and reducing the influences of the study design. The influences of several parameters on the distribution functions were analyzed. In a tiered approach those parameters inducing non-chemical related variability were subsequently excluded. In addition the distributions of EFs for two chemical categories with different toxicological potencies are analyzed to get a first impression on more chemical-specific EFs.

4.1 Tiered approach

4.1.1 Study level

We started with large datasets with a set of minimum requirements:

Narrow time frames close to the standard study durations were used, and study pairs with the same routes of administration and the same rodent species were compared.

The definition of the subacute time frame (20-33 days) excluded all 14-day studies conducted , e.g. under the US National Toxicology Program (NTP). These studies focus on dose finding and have only a limited scope of examination compared to standard subacute studies. Kalberlah and Schneider (1998) included these 14-day studies in their analyzis and mentioned that the results of these studies are difficult to compare with subchronic or chronic studies.

Our results (section 3.3.3) show that especially a comparable scope of examination is needed to derive a dataset with only the true chemical variability. Without the 14-day studies the amount of subacute studies from RepDose is reduced (subacute-to-chronic: 49 instead of 83 oral and 18 instead of 49 inhalation study pairs; subacute-to-subchronic: 78 instead of 145 oral and 31 instead of 74 inhalation study pairs), but a very likely source of additional variability is excluded by this decision. As a consequence the EFs for the extrapolation of subacute studies to longer durations are not applicable to 14-day studies.

Furthermore, inter-route differences were excluded in all datasets, as oral routes were not pooled but compared type by type: feed with feed, gavage with gavage etc. The LOEL of gavage studies is often determined by effects related to bolus application, whereas feed and drinking water result in a continuous exposure. Thus, an EF based on a gavage to feed comparison would additionally account for differences in administration being not chemical-related.

The EFs on the study level showed the widest spreads of values in all datasets (Table 1 and 2). Well evaluated chemicals are represented by a high number of studies in RepDose and thus provided several EFs per chemical at the study level. On average chemicals in our datasets have 2 EFs ranging from 1 to 13 EFs per chemical. Chemicals with many EFs may have a disproportionate statistical weight, which is called “chemical bias” in the following and is excluded in the next step of the tiered approach at the chemical level.

4.2.2 Chemical level

The analyzis of median EF per chemical reduces the data variability for chemicals having both high and low EFs and also the impact of chemicals with several similar low or high EFs. Our results indicate that the high spread of EFs in our datasets cannot be explained by the chemical bias as the distribution functions are similar to the study level for the majority of the datasets (Table 1 and 2). Only the small dataset oral, subacute-to-chronic showed a slight right shift due to the elimination of the chemical bias. This observation supports that the chemical bias can but must not have an impact on the EF distribution and should therefore be considered carefully.

4.2.3 Final level

Apart from the chemical bias discussed in the previous step, the EFs at the chemical level could not only account for the chemical-specific extrapolation over time but additional parameters may be included. Our analyzis of largest subset, the subchronic-to-chronic EFs, revealed that incongruent dose spacing, incomparable study pairs and unjustified LOAEL ratios lead to significantly changed distribution functions (Table 3). Considering these results at the final level datasets results in less widespread distribution functions depicting a more chemical-specific variability (Table 5). In order to further reduce the influence of dose spacing on the EFs, derivation of EFs based on BMDs instead on NOAELs would be desirable. Such an analyzis was not possible with our dataset. Additionally, in contrast to a N(L)OAEL/C, a BMD cannot be derived from every study which derives a NOAEL/C and a LOAEL/C as the data overall need to be suitable for modelling, e.g. sufficient number of dose groups and adequate dose selection to model dose response curve (Falk Filipsson and Victorin, 2003, Bokkers and Slob, 2005, Davis et al., 2010). Furthermore, the impact of the study design on the EFs is minimized but not completely eliminated by the selection of the most comparable study at the final level. The derivation of EF_{TO} is helpful to use studies which did not result in a NOAEL and thus did not cover the dose response curve completely. For such studies the derivation of a BMD is difficult or even not possible (Davis et al., 2010). Bokkers and Slob (2005) also had to exclude 40% of the available subchronic-to-chronic study pairs as an EF based on BMD could not be derived. In future more high quality data deriving a NOAEL or even a BMD may be publically available and the comparability of studies could be considered in a higher extent to get an improved analyzis.
The general chemical selection and their toxicological characteristics, however, are an inherent source of variability. Nevertheless, with this tiered approach we identified for the first time parameters influencing the EFs and derived final distributions with minimized additional variability.
In addition to these general considerations the final subacute-to-chronic datasets (oral and inhalation) are limited and less than one third of chemicals from the chemical level ratios based on comparable study pairs were found. Furthermore, the expected multiplicity of $EF_{subacute\text{-}to\text{-}subchronic} \times EF_{subchronic\text{-}to\text{-}chronic} = EF_{subacute\text{-}to\text{-}chronic}$ cannot be observed in our final-level dataset, but it is also hardly observed in the previously published datasets (Table 6). Unfortunately further elucidation is not possible due to the limited subacute-to-chronic dataset. The observation of the limited number of comparable studies, however, is also reflected in an ongoing scientific discussion about the conditions under which subacute-to-chronic extrapolation is appropriate (Kalberlah and Schneider 1998; Kramer et al. 1995). In general the limited number of inhalation studies impedes a conclusion on the final level subacute-to-subchronic and subacute-to-chronic extrapolation, while the details for the inhalation datasets are discussed later (section 4.5).

4.3 Chemical categories

It has to be discussed whether category specific EFs would differ from overall EFs. In the final level datasets surfactants as well as pesticides do not form distinct subsets but are similar to the overall

dataset, although data for both subsets is limited (Table 5). For the category of pesticides an analyzis by Zarn et al. (2010) recently revealed distributions for subchronic-to-chronic EFs for rats and mice which are in a similar range as our data.

Comparing the relative low toxicity of surfactants and relative high toxicity of pesticides gave rise to the hypothesis that toxicity might not have any influence on the EFs. The verification of this hypothesis as well as the derivation of substance-specific EFs would require larger datasets of highly comparable studies. Until now, any category-specific EF has not been able on being derived based on our dataset.

4.4 Comparison to published EF distributions

The discussion will focus on the comparison to comprehensive reviews prepared by Vermeire and Kalberlah (Vermeire et al. 1999 and 2001, Kalberlah and Schneider 1998, Kalberlah et al. 2002, Kalberlah et al. 2003). In Table 6 an overview on the distributions described in these publications is given and comments on several parameters which influence the published distributions are added. The results of Kalberlah et al. (2002) and Kalberlah and Schneider (1998) have higher GMs and 90th percentiles than our distributions but the GSDs are in a similar range. There is only very little overlap between the published data of the Kalberlah's group and our dataset, e.g. one chemical in the subchronic-to-chronic dataset of the NTP studies analyzed by Kalberlah and Schneider (1998). The subacute data used by Kalberlah's group include 14 day studies which are hardly comparable in scope to the longer term studies as they mentioned themselves. Furthermore, Kalberlah et al. (2002) and Kalberlah and Schneider (1998) include several ratios per chemical in their datasets which are based on a limited number of chemicals. Within our smallest dataset for subacute-to-chronic extrapolation we observed that this chemical bias can have an impact on the resulting distribution function. These differences in chemicals, EFs per chemical and study types do probably account for the differences in GMs and 90th percentiles. The parameters influencing the GSDs of our distributions are comparability of the studies and the dose spacing. As all datasets from Kalberlah and Schneider (1998) and Kalberlah et al. (2002) are based on studies from the same (NTP) or two different laboratories (agrochemicals) it is very likely that differences in dose spacing and scope of examination have already been minimized by the laboratories, thus it is likely that the GSDs are similar. The distributions calculated by Vermeire et al. (2001) are higher for GMs, GSDs and consequently also higher for the 90th percentiles than the final distributions we described. Vermeire et al. (2001) contained different and several possible sources of increased data variability: comparison of different species without allometric scaling, very broad time frames, no adjustment with regard to dose spacing and comparability of general study design. The chemicals included in the analyzis are not given. A comparison of the chemical domain is thus not possible. As none of the minimum requirements for selection of study pairs and none of the additionally identified sources of data variability is excluded by Vermeire et al. (2001) the shift and wider spread of the distributions is reasonable. The comparison

of our final distributions to the previously published datasets support the observation that the general requirements for study selection (same species, route, narrow time frames) and the use of comparable studies with similar dose spacing have significant impact on the distribution functions and the derived extrapolation factors. The application of default extrapolation, either deterministic or probabilistic, should thus be a case by case decision. The underlying distribution should be carefully selected with regard to the chemical domain and intrinsic properties of the substance (e.g. bioaccumulation potential).

4.5 Inhalation

The comparison of the distributions derived from inhalation studies to the corresponding distributions based on oral studies did not reveal significant differences on the study and chemical level, suggesting that there might be no need for route-specific EFs. At the study level as well as at the chemical level the EFs, however, are based on NOEC or LOEC ratios without discrimination of local or systemic effects triggering the study's LOEC and NOEC. Kalberlah et al. (2002) discussed that the correlation over time for local effects is not necessarily expected to be the same as for systemic effects. For the final-level dataset, only EFs based on systemic effects were analyzed, so that time extrapolation for systemic effects after oral and inhalation exposure were comparable. It turned out that only a very small number of NOAEC ratios were removed due to local effects. The majority of all inhalation studies (or chemicals) available were removed as there were not any comparable studies. Only one substance was removed due to local effects in the subacute-to-subchronic dataset and two EFs were recalculated based on systemic effects for the subchronic-to-chronic dataset. Thus, we can conclude that local effects do not predominantly trigger the LOAEC and NOAEC values of chemicals with comparable inhalation studies in RepDose. This might be a matter of selection of the chemicals, as the number of chemicals in all inhalation datasets is limited. Furthermore, because of the limited number of chemicals with local effects triggering the LOAEC and NOAEC we were not able to evaluate time extrapolation for locally acting substances. Our analyzis shows that for predominantly systemically active substances there is no need for different default time EFs for oral and inhalation exposures. The analyzis by Kalberlah et al. (2002) on locally active substances also stated that similar default factors as for systemic effects and oral administration are appropriate. Nevertheless, the application of default factors always has to be regarded as the last resort in the absence of more substance-specific information.

Acknowledgement:

The authors would like to thank H. Buist and D. Kroese from TNO (Utrechtseweg 48, NL-3704 HE Zeist) for the kindly provided ToxBase data. Furthermore, the authors would like to extend their thanks for the sponsoring of parts of the FhG database RepDose by CEFIC LRI, and the EU FP-6 project OSIRIS.

The work presented in this publication was funded by ERASM.

Conflict of Interest statement:

The authors declare that there are no conflicts of interest.

References

Bitsch A., Jacobi S., Melber C., Wahnschaffe U., Simetska N., Mangelsdorf I., 2006. REPDOSE: A database on repeated dose toxicity studies of commercial chemicals – A multifunctional tool. Regul. Toxicol. Pharmacol. 46, 202-210.

Bokkers, B.G., Slob, W., 2005. A comparison of ratio distribution based on the NOAEL and the benchmark approach for subchronic-to-chronic extrapolation. Tox. Sci. 85, 1033-1040.

Calabrese, E.J., Gilbert, C.E., 1993. Lack of total independence of uncertainty factors (UFs): implications for the size of the total uncertainty factor. Regul. Toxicol. Pharmacol. 17(1), 44-51.

Dourson, M.L., Stara, J.F., 1983. Regulatory History and Experimental Support of Uncertainty (Safety) Factors. Regul. Toxicol. Pharmacol. 3 (3), 224-238.

Davis, J.A., Gift, J.S., Zhao, Q.J., 2010. Introduction to benchmark dose methods and U.S. EPA's benchmark dose software (BMDS) version 2.1.1. Toxicol. Appl. Pharmacol. doi:10.1016/j.taap.2010.10.016.

Falk Filipsson, A., Victorin, K., 2003. Comparison of available benchmark dose softwares and models using trichloroethylene as a model substance. Regul Toxicol Pharmacol. 37(3),343-55.

Falk-Filipsson, A., Hanberg, A., Victorin, K., Warholm, M., Wallen, M., 2007. Assessment factors – Applications in health risk assessment of chemicals. Environ. Res. 104, 108-127.

Groeneveld, C.N., Pauulussen, J.J.G., Houben, G.F., Hakkert, B., 1998. Extrapolation for exposure duration in oral toxicity. TNO Nutrition and Food Research Institute, TNO report V98.276. Zeist, The Netherlands.

Kalberlah, F., Schneider, K., 1998. Quantifizierung von Extrapolationsfaktoren. Endbericht des Forschungsvorhabens Nr. 116 06 113 des Umweltbundesamtes. Schriftenreihe der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Fb 796. Wirtschaftsverlag NW, Bremerhaven.

Kalberlah, F., Föst, U., Schneider, K., 2002. Time extrapolation and interspecies extrapolation for locally acting substances in case of limited toxicological data. Ann. Occup. Hyg. 46, 175-185.

Kalberlah, F., Schneider, K., Schuhmacher-Wolz, U., 2003. Uncertainty in toxicological risk assessment for non-carcinogenic health effects. Regul. Toxicol. Pharmacol. 37, 92-104.

Kramer, H.J., Van den Ham, W.A., Slob, W., Pieters, M.N., 1996. Conversion Factors Estimating Indicative Chronic No-Observed-Adverse-Effect Levels from Short-Term Toxicity Data. Regul. Toxicol. Pharmacol. 23, 249-255.

Mohr, U., Dungworth, D.L., Capen, C.C. (Eds.), 1992 .Pathobiology of the aging rat Vol. 1 Blood and lymphoid, respiratory, urinary, cardiovascular, and reproductive systems. International Life Sciences Institute Washington, D. C.. ILSI Press

Vermeire, T., Stevenson, H., Peiters, M.N., Rennen, M., Slob, W., Hakkert, B.C., 1999. Assessment factors for human health risk assessment: a discussion paper. Crit. Rev. Toxicol. 29, 439-490.

Vermeire, T., Pieters, M., Rennen, M., Bos, P., 2001. Probabilistic assessment factors for human health risk assessment – A practical guide. TNO Nutrition and Food Research Institute, TNO report V3489. Zeist, The Netherlands.

Weil, C.S., 1972. Statistics vs safety factors and scientific judgement in the evaluation of safety for man. Toxicol. Appl. Pharmacol. 21, 454-463.

Zarn, J.A, Hänggi, E., Kuchen, A., Schlatter, J.R., 2010. The significance of the subchronic toxicity in the diatary risk assessment of pesticides. Regul. Toxicol. Pharmacol. 58, 72-78.

Figure 1: Normal distributions derived from the logarithms of N(L)OEL ratios for the three data sets on oral subchronic-chronic extrapolation, indicating 10^{th}, 50^{th}, and 90^{th} percentiles.

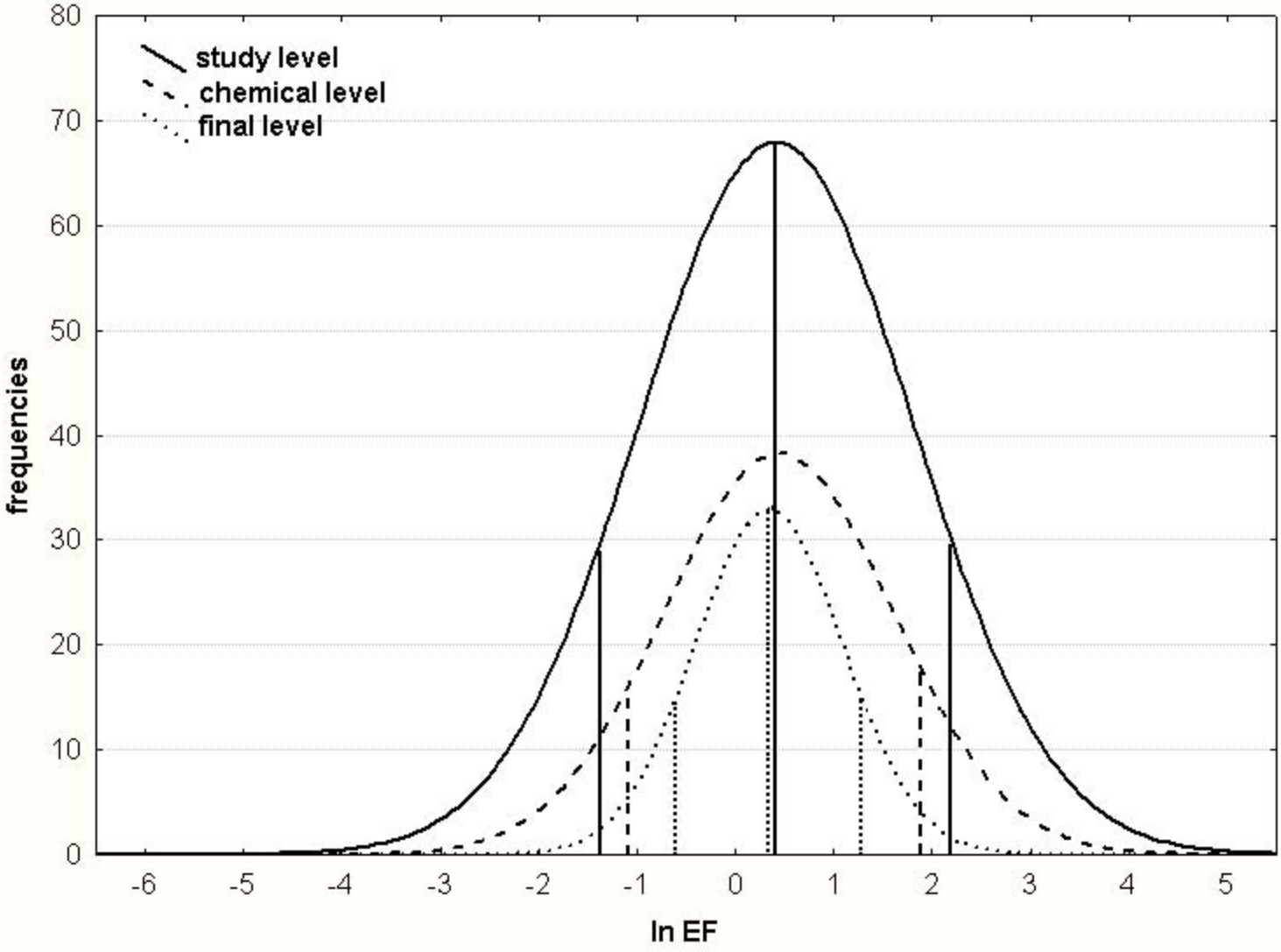
study level
chemical level
final level
frequencies
80
70
60
50
40
30
20
10
0
-6
-5
-4
-3
-2
-1
0
1
2
3
4
5
ln EF

Table 1: Descriptive statistics on EFs for oral exposure.

Extrapolation	Data set	N (N_{NOEL},N_{LOEL})	GM	GSD	Median	90^{th} percentile	95^{th} percentile
Subacute-subchronic	Study level	78 (23, 54)	2.5	5.2	1.9	20.7	37.6
	Chemical level	53 (20, 33)	2.4	5.1	2	19.4	35.0
Subacute- chronic	Study level	49 (24, 25)	2.9	4.9	2.8	22.2	39.6
	Chemical level	33 (14, 19)	4.1	3.9	2.8	23.5	38.5
Subchronic-chronic	Study level	236 (74, 162)	1.5	4.0	1.8	8.9	14.7
	Chemical level	111 (40, 61)	1.5	3.2	1.7	6.7	10.2

Table 2: Descriptive statistics for EFs for inhalation route.

Extrapolation	Data set	N(N_{NOEC},N_{LOEC})	GM	GSD	Median	90^{th} percentile	95^{th} percentile
Subacute-subchronic	Study level	31 (9, 22)	1.9	4.3	1.7	12.3	20.9
	Chemical level	23 (6, 17)	2.1	4.0	1.4	12.4	20.5
Subacute- chronic	Study level	18 (2, 16)	2.4	3.1	3.3	10.2	15.4
	Chemical level	15 (2, 13)	2.5	3.1	3.3	10.7	16.1
Subchronic-chronic	Study level	101 (14, 87)	1.6	3.8	1.5	8.9	14.4
	Chemical level	46 (9, 37)	2.0	3.3	1	9.2	14.3

Table 3: Influence of dose spacing, data quality, study comparability and target organ approach on the oral subchronic to chronic extrapolation factor.

Type of data set	Criteria		N	GM	GSD	Median	90th percentile	95th percentile
Study level	Dose spacing	Similar ($0.5<DS_{ratio}>2$)	37	1.5	4.1	1.6	9.2	15.3
		Different ($DS_{ratio}\leq 0.5$)	10	3.2	3.0	2.8	13.1	19.5
		Different ($DS_{ratio}\geq 2$)	11	0.3	3.6	0.4	1.5	2.5
	Data quality	Klimisch 1	67	1.6	3.2	2.0	7.1	10.8
		Klimisch 2	131	1.4	4.7	1.7	10.2	17.9
Chemical level	Comparable studies	NOEL ratios	39	1.3	2.2	1.3	3.6	4.8
		Respective chemical level	39	1.5	2.8	1.5	5.6	8.2
		Target organ NOEL ratios	19	1.7	1.9	2.0	3.9	4.9
		Respective chemical level	19	1.9	1.7	2.2	3.8	4.5
	No comparable studies	LOEL ratios	45	1.3	5.8	1.5	12.4	23.4
		NOEL ratios	8	3.6	5.3	2.9	30.5	55.9

Dose spacing (DS)=LOEL/NOEL; Dose spacing ratio (DS_{ratio})= $DS_{subchronic}/DS_{chronic}$; Comparable studies: comparable study design, same scope of examination, if possible same strain, same laboratory, same author; Respective chemical level: results of the analysis for the same chemicals at the chemical level (median of the EFs per chemical);

Table 4: Numbers of decisions taken to compile the final datasets.

Type of data set		Number of decisions N (N%)				Final level
		EF_{NOEL}	EF_{TO}	EF_{max}	EF_{DS}	Total (100%)
Oral	subacute-subchronic	24 (63)	4 (11)	10 (26)	-	38
	subacute-chronic	12 (86)	-	2 (14)	-	14
	subchronic-chronic	35 (60)	19 (33)	3 (5)	1 (2)	58
Inhalation	subacute-subchronic	5 (56)	4	-	-	9
	subacute-chronic	1 (25)	2 (50)	1 (25)	-	4
	subchronic-chronic	5 (26)	11 (58)	2 (11)	1 (5)	19

EF_{NOEL} - NOEL ratio; EF_{TO} – target organ NOEL ratio; EF_{max} – LOEL ratio maximum value option; EF_{DS} – LOEL ratio as less influenced by dose spacing differences than NOEL ratio;

Table 5: Descriptive statistics on final datasets for oral and inhalation and evaluation of category-specific EFs.

	Extrapolation	Data set	N	GM	GSD	Median	90th percentile	95th percentile
Oral	Subacute-subchronic	Final level	38	1.3	2.4	1.3	4.0	5.5
		Pesticides	7	1.4	2.5	1.3	4.5	6.3
		Minus pesticides	31	1.3	2.4	1.3	4.0	5.5
		Surfactants	12	1.6	1.9	1.8	3.6	4.6
		Minus surfactants	26	1.2	2.6	1.2	4.1	5.8
	Subacute-chronic	Final level	14	3.4	3.7	4.6	18.2	29.2
		Pesticides	8	5.0	2.3	7.3	14.5	19.7
		Minus pesticides	6	2.1	5.5	3.3	18.7	34.7
		Surfactants	1	2	-	-	-	-
		Minus surfactants	13	3.7	3.8	5.0	20.5	33.3
	Subchronic-chronic	Final level	58	1.4	2.1	1.5	3.6	4.7
		Pesticides	25	1.3	2	1.5	3.2	4.1
		Minus pesticides	33	1.5	2.3	1.5	4.5	5.9
		Surfactants	3	1.1	1.1	1.0	1.2	1.3
		Minus surfactants	55	1.4	2.2	1.6	3.8	5.1
Inhalation	Subacute-subchronic	Final level	9	1.4	4.1	1.8	8.5	14.3
		Surfactants	0	-	-	-	-	-
	Subacute-chronic	Final level	4	1.3	2.8	1.2	4.9	7.1
		Surfactants	0	-	-	-	-	-
	Subchronic-chronic	Final level	19	2.1	2.2	2	5.8	7.7
		Surfactants	3	1.5	-	1	-	-
Conclusion	Subchronic-chronic	Oral+inhalation	77	1.5	2.2	1.6	4.1	5.5

Table 6: Collection of time EFs described in literature.

Author	Duration	Species	Route	Ratio based on	N	GM	GSD	90%	Comments
Kalberlah & Schneider, 1998 (agrochemicals)	subacute-subchronic	rats or mice (matched)	oral	NOAEL	13	2.1	2.6	11.2	Only 13 chemicals but several ratios per chemical included (rats+mice); data from two companies only, no distinction between different oral applications
	subacute-chronic				16	5.3	3.3	27.3	
	subchronic-chronic				20	2.0	2.4	5.0	
Kalberlah & Schneider, 1998 (NTP)	subacute-subchronic	rats (similar results for mice not shown here)	gavage	NOAEL	41	2.8	2.1	6.8	NTP studies for 30 chemicals but several ratios per chemical (male+female)
	subacute-chronic				26	3.9	2.2	8.0	
	subchronic-chronic				22	2.5	1.9	6.6	
	subacute-subchronic			N(L)OAEL	87	3.3	n.a.	10	NTP studies for 30 chemicals but several ratios per chemical (male+female, NOAEL+LOAEL), no toxicological reasoning for LOAEL ratios
	subacute-chronic				76	5.1	n.a.	14.1	
	subchronic-chronic				71	2.9	n.a.	8.6	
Kalberlah et al., 2002 (NTP)	subacute-subchronic	rats or mice (matched)	inhalation	N(L)OAEL	106	3.3	n.a.	18.9	NTP studies for 46 chemicals but several ratios per chemical (rats+mice, male+female, NOAEL+LOAEL), no toxicological reasoning for LOAEL ratios
	subacute-chronic				59	7.2	n.a.	21.0	
	subchronic-chronic				68	2.7	n.a.	20.0	
Vermeire et al. 2001, Falk-Filipsson et al. 2007	subacute-subchronic	rats or mice (matched)	oral	NOAEL	35	2.0	4.0	11.8	Based on Groeneveld et al. 1998, no distinction between different oralapplications
	subacute-chronic	Rats, mice without matching or allometric scaling			117*	5.0	3.5	25.0	*Metaanalysis of 4 literature studies (N=20 to 71) with serveral different deficiencies: variable and broad time frames, interspecies variation (comparison of rats with mice without matching or allometric scaling), no distinction between different oral applications
	subchronic-chronic	Rats, mice and dogs without matching or allometric scaling			419*	2.0	3.5	10.0	*Metaanalysis of 11 literature studies (N=9 to 149); Serveral different deficiencies within the studies: variable and broad time frames, interspecies variation (comparison of rats with mice without matching or allometric scaling), no distinction between different oral applications, old data

N – Number of ratios analyzed; GM – geometric mean, GSD – geometric standard deviation; 90% - 90th percentile; n.a. value/information not available

Distribution analysis with @risk for the oral. subchronic-to-chronic extrapolation. Empircal data (Input) and the calculated data for different distributions are given. The quality of fit is indicated by Chi^2 (Chi-Sq). Anderson-Darling (A-D) and Kolmogorov-Smirnov (K-S) statistics.

Study level									
	Input	Lognorm	Weibull	LogLogistic	Pearson6	Expon	InvGauss	Triang	Uniform
Mean	3.287	3.8079	3.2156	5.6064	3.3304	3.287	3.287	18.6505	27.9622
Median	1.7898	1.4629	1.7854	1.5571	1.635	2.2784	0.7409	16.3885	27.9622
Std. Deviation	5.5315	9.1513	4.0733	+Infinity	7.6904	3.287	8.9677	13.1842	16.144
10%	0.2594	0.2485	0.1676	0.2889	0.2511	0.3463	0.1514	2.8757	5.5924
25%	0.6173	0.5755	0.5918	0.6707	0.6583	0.9456	0.2927	7.4992	13.9811
50%	1.78	1.4629	1.7854	1.5571	1.635	2.2784	0.7409	16.3885	27.9622
75%	3.75	3.7188	4.2632	3.6153	3.6851	4.5567	2.3512	27.9731	41.9434
90%	7.9999	8.6115	8.0619	8.3939	7.4352	7.5686	7.4463	38.2526	50.332
95%	11.7197	14.2339	11.2189	14.8859	11.3656	9.8469	14.5363	43.4334	53.1282
Chi-Sq Statistic		24.0678	24.2034	26.1017	27.322	39.2542	83.7288	993.8305	1895.9322
P-Value		0.064	0.0617	0.037	0.0262	0.0006	0	0	0
A-D Statistic		1.0926	1.5349	0.7148	0.3005	6.8563	23.5091	304.3628	449.5521
P-Value		N/A	< 0.01	N/A	N/A	< 0.001	N/A	N/A	N/A
K-S Statistic		0.0672	0.0686	0.0586	0.0421	0.1268	0.2482	0.6809	0.7655
P-Value		N/A	< 0.01	N/A	N/A	< 0.01	N/A	N/A	N/A
Chemical level									
	Input	Pearson6	LogLogistic	Lognorm	Expon	Weibull	InvGauss	Triang	Uniform
Mean	2.6372	2.6423	3.4777	2.9291	2.6372	2.6333	2.6372	6.7508	10.0909
Median	1.7427	1.654	1.5926	1.5072	1.828	1.7834	0.9694	5.9327	10.0909
Std. Deviation	3.2041	3.4202	+Infinity	4.8813	2.6372	2.7102	5.0638	4.7682	5.826
10%	0.3333	0.3469	0.3953	0.344	0.2779	0.2566	0.2286	1.0456	2.0182
25%	0.75	0.77	0.7934	0.6926	0.7587	0.7215	0.4224	2.7178	5.0455
50%	1.7427	1.654	1.5926	1.5072	1.828	1.7834	0.9694	5.9327	10.0909
75%	3.4178	3.2752	3.1967	3.2798	3.6559	3.6394	2.563	10.1224	15.1364
90%	5.8509	5.8424	6.4164	6.6036	6.0723	6.1347	6.3985	13.8401	18.1636
95%	6.9	8.2154	10.3063	10.0385	7.9003	8.0427	10.7468	15.7138	19.1727
Chi-Sq Statistic		12.5676	9.973	10.1892	9.5405	8.8919	38.9459	144.2432	325.4324
P-Value		0.3225	0.5328	0.5135	0.5721	0.6319	0.0001	0	0
A-D Statistic		0.1696	0.3592	0.5861	0.7182	0.7254	7.7399	57.8226	114.3688
P-Value		N/A	N/A	N/A	> 0.25	0.05 <= p <=	N/A	N/A	N/A

K-S Statistic		0.0479	0.0573	0.0654	0.0911	0.1 0.0858	0.2119	0.4759	0.6362
P-Value		N/A	N/A	N/A	0.1 <= p <= 0.15	0.025 <= p <= 0.05	N/A	N/A	N/A
Final level									
	Input	Lognorm	LogLogistic	Pearson6	InvGauss	Weibull	Expon	Triang	Uniform
Mean	1.8311	1.7993	1.8381	1.8013	1.8311	1.8527	1.8311	4.5207	6.614
Median	1.475	1.3761	1.3874	1.3737	1.3478	1.49	1.2692	3.9914	6.614
Std. Deviation	1.8615	1.5158	2.2412	1.6089	1.5782	1.48	1.8311	3.0894	3.8186
10%	0.5	0.5383	0.5738	0.5488	0.5245	0.3342	0.1929	0.8259	1.3228
25%	1	0.8397	0.8922	0.8519	0.8045	0.7415	0.5268	1.909	3.307
50%	1.45	1.3761	1.3874	1.3737	1.3478	1.49	1.2692	3.9914	6.614
75%	2	2.2551	2.1573	2.2187	2.3081	2.5825	2.5384	6.7053	9.9211
90%	3.1	3.5176	3.3546	3.4578	3.7224	3.8627	4.2162	9.1134	11.9053
95%	4	4.5898	4.5294	4.5536	4.8961	4.7597	5.4854	10.3271	12.5667
Chi-Sq Statistic		9.9655	12.7586	12.7586	24.8621	31.6897	34.7931	84.7586	151.7931
P-Value		0.2675	0.1204	0.1204	0.0016	0.0001	0	0	0
A-D Statistic		0.6887	0.5617	0.6408	0.9009	1.7894	3.4323	29.7677	55.2583
K-S Statistic		0.132	0.1068	0.127	0.1511	0.1593	0.2249	0.5311	0.6794
P-Value		N/A	N/A	N/A	N/A	< 0.01	< 0.01	N/A	N/A

This table summarizes all studies used in the tiered approach. For each chemical the category (subacute-subchronic – 1; subacute-chronic – 2; subchronic-chronic – 3), species and route is given including the references for the distinct studies. For further details on the studies one may refer to the publicly available version of RepDose: www.fraunhofer-repdose.de. Within the columns “study level” and “final level” it is indicated by “x” when the study pair is included in the dataset. The chemical level dataset consists of the median of all EFs per chemical for the same category. The structural category indicates pesticides as "p" and surfactants as "s".

CAS	Name	Category	Species	Route	shortterm author	shortterm year	longterm author	longterm year	study level	final level	structural category
50-00-0	Formaldehyde	3	rat	inhalation	Zwart, A, et al. Woutersen, RA, et al. Feron, VJ, et al.	1988 1987 1988	Woutersen, RA, et al.	1989	x		
50-00-0	Formaldehyde	3	rat	inhalation	Zwart, A, et al. Woutersen, RA, et al. Feron, VJ, et al.	1988 1987 1988	Kerns, WD, et al.	1983	x		
50-00-0	Formaldehyde	3	rat	inhalation	Zwart, A, et al. Woutersen, RA, et al. Feron, VJ, et al.	1988 1987 1988	Sellakumar et al.	1985	x		
50-00-0	Formaldehyde	3	rat	inhalation	Zwart, A, et al. Woutersen, RA, et al. Feron, VJ, et al.	1988 1987 1988	Kerns W.D.et al.	1983	x		
50-00-0	Formaldehyde	3	rat	inhalation	Feron, VJ, et al.	1988	Woutersen, RA, et al.	1989	x	x	
50-00-0	Formaldehyde	3	rat	inhalation	Feron, VJ, et al.	1988	Kerns, WD, et al.	1983	x		
50-00-0	Formaldehyde	3	rat	inhalation	Feron, VJ, et al.	1988	Sellakumar et al.	1985	x		
50-00-0	Formaldehyde	3	rat	inhalation	Feron, VJ, et al.	1988	Kerns W.D.et al.	1983	x		
50-00-0	Formaldehyde	3	rat	inhalation	Zwart et al.	1988	Woutersen, RA, et al.	1989	x		
50-00-0	Formaldehyde	3	rat	inhalation	Zwart et al.	1988	Kerns, WD, et al.	1983	x		
50-00-0	Formaldehyde	3	rat	inhalation	Zwart et al.	1988	Sellakumar et al.	1985	x		
50-00-0	Formaldehyde	3	rat	inhalation	Zwart et al.	1988	Kerns W.D.et al.	1983	x		
50-00-0	Formaldehyde	2	rat	drinking	Til et al.	1987	Til, HP, et al.	1989	x		

				water						
50-00-0	Formaldehyde	2	rat	drinking water	Til et al.	1987	Tobe et al.	1989	x	x
50-00-0	Formaldehyde	1	rat	drinking water	Til et al.	1987	Johannsen et al	1986	x	
50-00-0	Formaldehyde	3	rat	drinking water	Johannsen et al.		Til, HP, et al.	1989	x	
50-00-0	Formaldehyde	3	rat	drinking water	Johannsen et al.		Tobe et al.	1989	x	
51-03-6	Piperonyl butoxide	2	rat	feed	Modeweg-Hansen et al.	1984	NTP (US)	1979	x	
51-03-6	Piperonyl butoxide	1	rat	feed	Modeweg-Hansen et al.	1984	Maekawa et al.	1985	x	
51-03-6	Piperonyl butoxide	1	rat	feed	Modeweg-Hansen et al.	1984	Fujitani et al	1992	x	
51-03-6	Piperonyl butoxide	2	rat	feed	Modeweg-Hansen et al.	1984	Sarles and Vandergrift	1952	x	
51-03-6	Piperonyl butoxide	2	rat	feed	Modeweg-Hansen et al.	1984	JMPR	1995	x	
51-03-6	Piperonyl butoxide	3	rat	feed	Maekawa et al.	1985	NTP (US)	1979	x	
51-03-6	Piperonyl butoxide	3	rat	feed	Maekawa et al.	1985	Sarles and Vandergrift	1952	x	
51-03-6	Piperonyl butoxide	3	rat	feed	Maekawa et al.	1985	Graham	1987	x	
51-03-6	Piperonyl butoxide	3	rat	feed	Fujitani et al	1992	NTP (US)	1979	x	
51-03-6	Piperonyl butoxide	3	rat	feed	Fujitani et al	1992	Sarles and Vandergrift	1952	x	
51-03-6	Piperonyl butoxide	3	rat	feed	Fujitani et al	1992	Graham	1987	x	
51-03-6	Piperonyl butoxide	2	rat	feed	Modeweg-Hansen et al.	1984	Graham et al	1987		x
51-03-6	Piperonyl butoxide	1	rat	feed	Modeweg-Hansen et al.	1984	Fujitani et al.	1992		x
55-31-2	1-Epinephrine Hydrochloride	3	mouse	inhalation	NTP (US)	1990	NTP (US)	1990	x	
55-31-2	1-Epinephrine	3	rat	inhalation	NTP (US)	1990	NTP (US)	1990	x	

	Hydrochloride										
55-38-9	Fenthion	2	mouse	feed	Leser	1990	Suberg and Leser	1990	x		
55-38-9	Fenthion	3	rat	feed	Shimamoto and Hattori	1969	Bomhard and Loser	1977	x	x	p
55-38-9	Fenthion	3	rat	feed	Shimamoto and Hattori	1969	Christenson	1990	x		
56-38-2	Parathion	1	mouse	feed	Ramundo J	1979	Daly	1980	x		
56-38-2	Parathion	1	mouse	feed	Ramundo J	1979	Daly	1980		x	p
56-38-2	Parathion	3	rat	feed	Daly	1980	Daly	1984	x		
56-38-2	Parathion	3	rat	feed	Daly	1980	Eiben	1987	x	x	p
58-55-9	Theophylline	3	rat	gavage	NTP (US) Collins, JJ et al.	1998 1988	NTP (US)	1998	x		
58-89-9	Lindane	3	rat	feed	CIEL (Centre International d'Etudes du Lindane),	1983	WHO	1991	x		
58-89-9	Lindane	1	rat	feed	Doisy and Bocklage et al.	1950	CIEL (Centre International d'Etudes du Lindane),	1983	x		
58-89-9	Lindane	2	rat	feed	Doisy and Bocklage	1949, 1950	WHO	1991	x		
58-89-9	Lindane	1	rat	feed	Doisy and Bocklage et al.	1950	van Velsen et al.	1984	x		
58-89-9	Lindane	3	rat	feed	van Velsen et al.	1984	WHO	1991	x	x	
59-87-0	Nitrofurazone	3	mouse	feed	NTP (US) Kari, FW et al.	1988 1989	NTP (US) Kari, FW et al.	1988 1989	x		
59-87-0	Nitrofurazone	3	rat	feed	NTP (US) Kari, FW et al.	1988 1989	NTP (US) Kari, FW et al.	1988 1989	x		
61-82-5	Amitrol	2	rat	feed	Bayer AG,	1983	Steinhoff, DH, Weber, H & Mohr, U	1983	x		
61-82-5	Amitrol	2	rat	feed	Bayer AG,	1983	EHC 158		x	x	
61-82-5	Amitrol	2	rat	feed	Bayer AG,	1983	EHC 158		x		
61-82-5	Amitrol	2	rat	inhalation	Cox und Re	1978	Becci	1983	x		
61-82-5	Amitrol	2	rat	feed	EHC 158		Steinhoff, DH, Weber, H & Mohr, U	1983	x		
61-82-5	Amitrol	2	rat	feed	EHC 158		EHC 158		x		
61-82-5	Amitrol	2	rat	feed	EHC 158		EHC 158		x		
61-82-5	Amitrol	2	rat	feed	Babish	1977	Steinhoff, DH, Weber, H &	1983	x		

							Mohr, U			
61-82-5	Amitrol	2	rat	feed	Babish	1977	EHC 158		x	
61-82-5	Amitrol	2	rat	feed	Babish	1977	EHC 158		x	
64-17-5	Ethanol	2	mouse	drinking water	NTP (US)	1996	NTP (US)	1996	x	
67-63-0	2-Propanol	3	rat	inhalation	Burleigh-Flayer, H et al. Gill, M et al.	1998 1994	Burleigh-Flayer, H et al. Garman, R et al.	1997 1995	x	
67-63-0	2-Propanol	3	rat	inhalation	Nakaseko, H	1991	Burleigh-Flayer, H et al. Garman, R et al.	1997 1995	x	
67-63-0	2-Propanol	3	rat	inhalation	Burleigh-Flayer, HD et al.	1994	Garman, R et al. Burleigh-Flayer, H et al.	1995 1997	x	
67-63-0	2-Propanol	3	rat	inhalation	Burleigh-Flayer, HD et al.	1994	Garman, R et al. Burleigh-Flayer, H et al.	1995 1997		x
67-66-3	Chloroform	1	rat	drinking water	Larson, JL, et al.	1995	Jorgenson and Rushbrook	1980	x	
67-66-3	Chloroform	1	rat	inhalation	Plummer et al.	1990	Templin, MV, et al.	1996	x	
67-66-3	Chloroform	1	rat	drinking water	Chu et al.	1982	Jorgenson and Rushbrook	1980	x	
67-66-3	Chloroform	1	rat	gavage	Chu et al.	1982	Chu et al.	1982		x
67-72-1	Hexachloroethane	3	rat	gavage	NTP (US)	1989	NTP (US)	1989	x	
71-55-6	1,1,1-Trichloroethane	3	rat	inhalation	Blohm, M, et al.	1985	Quast, JF, et al.	1988	x	x
74-83-9	Methyl bromide	3	mouse	inhalation	NTP (US)	1992	NTP (US)	1992	x	
74-83-9	Methyl bromide	3	rat	inhalation	NTP (US)	1992	Gotoh, K et al.	1994	x	
74-83-9	Methyl bromide	3	rat	inhalation	NTP (US)	1992	Reuzel, PGJ et al.	1991	x	
74-83-9	Methyl bromide	3	mouse	inhalation	Morissey, RE et al.	1988	NTP (US)	1992	x	
74-83-9	Methyl bromide	3	rat	inhalation	Morissey, RE et al.	1988	Gotoh, K et al.	1994	x	
74-83-9	Methyl bromide	3	rat	inhalation	Morissey, RE et al.	1988	Reuzel, PGJ et al.	1991	x	
74-96-4	Ethyl bromide	3	mouse	inhalation	NTP (US)	1989	NTP (US)	1989	x	
74-96-4	Ethyl bromide	3	rat	inhalation	NTP (US)	1989	NTP (US)	1989	x	
75-00-3	Chloroethane	3	mouse	inhalation	NTP (US)	1989	NTP (US)	1989	x	
75-00-3	Chloroethane	3	rat	inhalation	NTP (US)	1989	NTP (US)	1989	x	

75-05-8	Acetonitrile	3	rat	inhalation	NTP (US)	1994	NTP (US)	1994	x	x
75-05-8	Acetonitrile	3	rat	inhalation	EPA Report Coate, WB; Hazelton Laboratorie	1987 1983	NTP (US)	1994	x	
75-07-0	Acetaldehyde	2	rat	inhalation	Appelman, LM et al.	1982	Woutersen, RA & Feron, VJ Woutersen, RA	1987 1986	x	
75-07-0	Acetaldehyde	2	rat	inhalation	Appelman et al.	1986	Woutersen, RA Woutersen, RA & Feron, VJ	1986 1987	x	
75-09-2	Methylene chloride	3	rat	inhalation	Leuschner et al.	1984	NTP (US)	1986	x	
75-09-2	Methylene chloride	3	rat	inhalation	NTP	1986	NTP (US)	1986	x	
75-09-2	Methylene chloride	3	mouse	inhalation	NTP	1986	NTP (US)	1986	x	
75-09-2	Methylene chloride	3	mouse	inhalation	NTP	1986	NTP Mennear et al.	1986 1988	x	
75-09-2	Methylene chloride	3	rat	drinking water	Bornmann and Loeser	1967	NCA (Nat. Coffee Assoc.), Hazleton Laboratories	1982	x	
75-09-2	Methylene chloride	3	rat	drinking water	Kirschman et al.	1986	NCA (Nat. Coffee Assoc.), Hazleton Laboratories	1982	x	
75-15-0	Carbon disulfide	1	rat	inhalation	Szendzikowski, S. et al.	1973	Gottfried, MR, et al.	1985	x	
75-21-8	Ethylene oxide	2	rat	gavage	Hollingsworth, et al.	1956	Dunkelberg, H,	1982	x	x
75-21-8	Ethylene oxide	3	rat	inhalation	Mori, K, et al. Fujishiro, K, et al.	1990 1990	Snellings, WM, et al. Lynch, DW, et al. Garman, R, et al.	1984 1984 1985	x	
75-27-4	Bromodichloromethane	3	rat	gavage	NTP (US National Toxicology Programm)	1987	NTP (US)	1987	x	
75-27-4	Bromodichloromethane	3	mouse	gavage	NTP (US)	1987	NTP (US)	1987	x	
75-27-4	Bromodichloromethane	3	mouse	gavage	NTP (US)	1987	NTP (US)	1987		x
75-27-4	Bromodichloromethane	3	mouse	gavage	NTP (US)	1987	NTP (US)	1987	x	
75-27-4	Bromodichlorome	3	mouse	gavage	NTP (US)	1987	NTP (US)	1987	x	

	thane									
75-27-4	Bromodichloromethane	3	mouse	gavage	NTP (US)	1987	NTP (US)	1987	x	
75-35-4	1,1-Dichloroethene	3	rat	gavage	NTP (US)	1982	NTP (US)	1982	x	
75-35-4	1,1-Dichloroethene	3	mouse	gavage	NTP (US)	1982	NTP (US)	1982	x	
75-35-4	1,1-Dichloroethene	1	rat	gavage	Siegers et al.	1983	NTP (US)	1982	x	
75-35-4	1,1-Dichloroethene	2	rat	gavage	Siegers et al.	1983	NTP (US)	1982	x	
75-52-5	Nitromethane	3	rat	inhalation	NTP (US)	1997	NTP (US)	1997		x
75-52-5	Nitromethane	3	rat	inhalation	NTP (US)	1997	NTP (US)	1997	x	
75-52-5	Nitromethane	3	rat	inhalation	NTP (US)	1997	Griffin, TB et al.	1996	x	
75-52-5	Nitromethane	3	mouse	inhalation	NTP (US)	1997	NTP (US)	1997	x	
75-65-0	tert-Butyl alcohol	3	mouse	drinking water	NTP (US) Lindamood, C III et al.	1995 1992	NTP (US) Cirvello, JD et al.	1995 1995	x	
75-65-0	tert-Butyl alcohol	3	rat	drinking water	Takahashi, K et al. NTP US Lindamood, C III et al.	1993 1995 1992	NTP (US) Cirvello, JD et al.	1995 1995	x	
76-01-7	Pentachloroethane	2	rat	gavage	NTP (US)	1996	NTP (US)	1983	x	
76-13-1	1,1,2-Trichloro-1,2,2-trifluoroethane	2	rat	inhalation	ITL,	1968	Trochimowicz HJ et al.	1988	x	
77-47-4	Hexachlorocyclopentadiene	3	mouse	inhalation	NTP (US)	1994	NTP (US)	1994	x	
77-47-4	Hexachlorocyclopentadiene	3	rat	inhalation	NTP (US)	1994	NTP (US)	1994	x	
78-59-1	Isophorone	3	rat	gavage	NTP (US)	1986	NTP (US)	1986	x	
78-59-1	Isophorone	3	mouse	gavage	NTP (US)	1986	NTP (US)	1986	x	
78-87-5	1,2-Dichloropropane	3	rat	gavage	Johnson, KA, Gorzinski, SJ	1988	NTP (US)	1986	x	
78-87-5	1,2-Dichloropropane	3	rat	gavage	NTP (US)	1986	NTP (US)	1986	x	
78-87-5	1,2-	3	rat	gavage	Bruckner, JW, et al.	1989	NTP (US)	1986	x	

	Dichloropropane									
78-87-5	1,2-Dichloropropane	3	mouse	gavage	NTP (US)	1986	NTP (US)	1986		
78-93-3	Methyl Ethyl Ketone	1	rat	inhalation	Toftgard et al.	1981	Cavender FL, et al.	1983	x	
78-93-3	Methyl Ethyl Ketone	1	rat	inhalation	Nilsen and Toftgard	1980	La Belle and Brieger	1955		
79-06-1	Acrylamide	3	rat	drinking water	Burek, et al.	1980	Johnson,	1986	x	x
79-06-1	Acrylamide	3	rat	drinking water	Burek, et al.	1980	Friedman, 1995 American Cyanamid, 1989	1995	x	
79-11-8	Chloroacetic acid	3	mouse	gavage	NTP (US)	1992	NTP (US)	1992		x
79-21-0	Peroxyacetic acid	1	mouse	inhalation	Merka, V, Urban R	1976	Heinze, (Nattermann)	1984	x	
79-22-1	Methyl chloroformate	1	rat	inhalation	HRC	1992	BASF	1999	x	
79-43-6	Dichloroacetic acid	3	rat	drinking water	Mather C. G. et al.	1990	De Angelo et al.	1996	x	
80-05-7	Bisphenol A	3	mouse	feed	NTP (US)	1982	NTP (US)	1982	x	
80-05-7	Bisphenol A	3	mouse	feed	Furukawa	1994	NTP (US)	1982	x	
80-07-9	p,p-Dichlorodiphenyl sulfone	3	rat	feed	NTP (US) NTP (US)	2001 2006	NTP (US) NTP (US)	2001 2006	x	x
80-07-9	p,p-Dichlorodiphenyl sulfone	3	mouse	feed	NTP (US) NTP (US)	2001 2006	NTP (US) NTP (US)	2001 2006	x	
80-62-6	Methyl methacrylate	3	rat	inhalation	NTP (US)	1986	NTP (US)	1986	x	
80-62-6	Methyl methacrylate	3	rat	inhalation	NTP (US)	1986	NTP (US)	1986	x	
80-62-6	Methyl methacrylate	3	mouse	inhalation	NTP (US)	1986	NTP (US)	1986	x	
81-49-2	1-Amino-2,4-dibromoanthraquinone	3	rat	feed	NTP (US) NTP (US)	1996 2004	NTP (US) NTP (US)	1996 2004	x	
81-49-2	1-Amino-2,4-dibromoanthraquinone	3	mouse	feed	NTP (US) NTP (US)	1996 2004	NTP (US) NTP (US)	1996 2004	x	

82-68-8	Pentachloronitrobenzene	3	rat	feed	Finnegan et al.	1958	Sinkeldam et al.	1974	x	
82-68-8	Pentachloronitrobenzene	3	rat	feed	Finnegan et al.	1958	Goldenthal	1991	x	
82-68-8	Pentachloronitrobenzene	3	rat	feed	Hoescht AG	1964	Sinkeldam et al.	1974	x	
82-68-8	Pentachloronitrobenzene	3	rat	feed	Hoescht AG	1964	Goldenthal	1991	x	
82-68-8	Pentachloronitrobenzene	3	rat	feed	McGee	1988	Sinkeldam et al.	1974	x	
82-68-8	Pentachloronitrobenzene	3	rat	feed	McGee	1988	Goldenthal	1991	x	
82-68-8	Pentachloronitrobenzene	3	mouse	feed	NTP	1987	NTP	1987	x	
84-65-1	9,10-Anthraquinone	3	mouse	feed	NTP (US)	2005	NTP (US)	2005	x	
84-65-1	9,10-Anthraquinone	3	rat	feed	NTP (US)	2005	NTP (US)	2005	x	
84-74-2	Di-n-butyl phthalate	1	rat	feed	BIBRA The British Industrial Biological Research Association Barber, ED et al.	1986 1987	NTP (US)	1995	x	
84-74-2	Di-n-butyl phthalate	1	rat	feed	BIBRA The British Industrial Biological Research Association Barber, ED et al.	1986 1987	NTP (US)	1995	x	
84-74-2	Di-n-butyl phthalate	1	rat	feed	BIBRA (The British Industrial Biological Research Association Barber, ED et al.	1986 1987	NTP (US)	1995	x	
84-74-2	Di-n-butyl phthalate	1	rat	feed	BIBRA (The British Industrial Biological Research Association Barber, ED et al.	1986 1987	NTP (US)	1995	x	x
84-74-2	Di-n-butyl phthalate	1	rat	feed	Bell, FP et al.	1978	NTP (US)	1995	x	
84-74-2	Di-n-butyl phthalate	1	rat	feed	Bell, FP et al.	1978	NTP (US)	1995	x	

85-68-7	Butyl benzyl phthalate	1	rat	feed	Barber, ED et al.	1987	Hammond, BG et al.	1987	x	
85-68-7	Butyl benzyl phthalate	1	rat	feed	Barber, ED et al.	1987	Hammond, BG et al.	1987	x	
85-68-7	Butyl benzyl phthalate	2	rat	feed	Barber, ED et al.	1987	NTP (US)	1997	x	
85-68-7	Butyl benzyl phthalate	1	rat	feed	Barber, ED et al.	1987	NTP (US)	1981	x	
85-68-7	Butyl benzyl phthalate	3	rat	feed	Hammond, BG et al.	1987	NTP (US)	1997	x	
85-68-7	Butyl benzyl phthalate	3	rat	feed	Hammond, BG et al.	1987	NTP (US)	1997		x
85-68-7	Butyl benzyl phthalate	3	rat	feed	Hammond, BG et al.	1987	NTP (US)	1997	x	
85-68-7	Butyl benzyl phthalate	1	rat	inhalation	Hammond, BG et al.	1987	Monsanto	1982	x	x
85-68-7	Butyl benzyl phthalate	3	rat	feed	NTP (US)	1981	NTP (US)	1997	x	
87-68-3	Hexachloro-1,3-butadiene	2	rat	feed	Kociba, RJ et al., Dow Chemicals	1971	Kociba, RJ, et al.	1977	x	x
87-86-5	Pentachlorophenol	3	rat	feed	Johnson, RL, et al.	1973	NTP (US)	1997	x	
88-12-0	N-Vinyl-2-pyrrolidinone	3	rat	inhalation	Klimisch et al. BASF	1997 1986	Klimisch et al. BASF	1997 1992	x	
88-72-2	o-Nitrotoluene	3	mouse	feed	NTP (US)	1992	NTP (US)	2002	x	
88-72-2	o-Nitrotoluene	3	rat	feed	NTP (US)	1992	NTP (US)	2002	x	
88-72-2	o-Nitrotoluene	3	rat	feed	NTP (US)	1996	NTP (US)	2002	x	
88-85-7	2-(1-Methylpropyl)-4,6-dinitrophenol	1	rat	feed	Spencer HC	1948	Hoechst AG, Pharma Forschung Toxikologie und Pathologie	1987	x	
88-85-7	2-(1-Methylpropyl)-4,6-dinitrophenol	1	rat	feed	Linder RE	1986	Hoechst AG, Pharma Forschung Toxikologie und Pathologie	1987	x	x
89-78-1	Menthol (D/L-Menthol)	3	rat	feed	Tracor Jitko I	1976	NCI (National Cancer Institute, USA)	1979	x	
89-78-1	Menthol (D/L-Menthol)	3	mouse	feed	Tracor Jitko I	1976	NCI (National Cancer Institute, USA)	1979	x	

91-17-8	Decalin	3	mouse	inhalation	NTP (US)	2005	NTP (US)	2005	x	
91-17-8	Decalin	3	rat	inhalation	MacEwen JD & Vernot EH Gaworski et al.	1979 1985	NTP (US)	2005	x	
91-17-8	Decalin	3	rat	inhalation	NTP (US)	2005	NTP (US)	2005	x	
91-23-6	o-Nitroanisole	3	mouse	feed	NTP (US)	1993	NTP (US)	1993	x	
91-23-6	o-Nitroanisole	3	rat	feed	NTP (US)	1993	NTP (US)	1993	x	
93-15-2	Methyleugenol	3	rat	gavage	NTP (US) NTP (US)	2000 2004	NTP (US) NTP (US)	2004 2000	x	
93-15-2	Methyleugenol	3	mouse	gavage	NTP (US) NTP (US)	2000 2004	NTP (US) NTP (US)	2000 2004	x	
94-75-7	2,4-Dichlorophenoxy acetic acid	3	rat	feed	Task Force 2,4-D,	1983	Task Force 2,4-D,	1986	x	x
94-75-7	2,4-Dichlorophenoxy acetic acid	3	mouse	feed	Task Force 2,4-D,	1983	Task Force 2,4-D,	1986	x	
94-75-7	2,4-Dichlorophenoxy acetic acid	3	rat	feed	Task Force 2,4-D	1990	Task Force 2,4-D,	1986	x	
95-48-7	o-Cresol	1	rat	feed	NTP (US)	1992	NTP (US)	1992	x	
95-48-7	o-Cresol	1	rat	feed	NTP (US)	1992	NTP (US)	1992		x
95-48-7	o-Cresol	1	rat	feed	NTP (US)	1992	EHC 168		x	
95-48-7	o-Cresol	1	rat	feed	NTP (US)	1992	EHC 168		x	
95-48-7	o-Cresol	1	rat	feed	NTP (US)	1992	EHC 168		x	
95-48-7	o-Cresol	1	mouse	feed	NTP (US)	1992	NTP (US)	1992	x	
95-50-1	1,2-Dichlorobenzene	3	rat	gavage	Robinson, M	1991	NTP (US)	1985	x	
95-50-1	1,2-Dichlorobenzene	3	rat	gavage	NTP (US)	1985	NTP (US)	1985	x	
95-50-1	1,2-Dichlorobenzene	3	mouse	gavage	NTP (US)	1985	NTP (US)	1985	x	
95-80-7	2,4-Diaminotoluene	2	rat	feed	Varma, SK, et al. Thysen, B, et al.	1988 1985	NCI (Nat. Cancer Inst.), Cardy, RH,	1979 1979	x	
96-18-4	1,2,3-Trichloropropane	3	rat	gavage	Merrick, BA, et al.	1991	NTP (US)	1991	x	

96-33-3	Methyl acrylate	3	rat	inhalation	Klimisch, HJ et al., BASF AG	1978	Klimisch, HJ, Reininghaus, W	1984	x	
98-00-0	Furfuryl alcohol	3	rat	inhalation	NTP (US)	1999	NTP (US)	1999	x	
98-00-0	Furfuryl alcohol	3	mouse	inhalation	NTP (US)	1999	NTP (US)	1999	x	
98-56-6	p-Chlorobenzotrifluoride	1	rat	gavage	Macri, A et al.	1987	Lilly Research Laboratories (LRL)	1983	x	x
98-83-9	(alpha)-Methylstyrene	3	rat	inhalation	NTP (US)	2007	NTP (US)	2007	x	
98-83-9	(alpha)-Methylstyrene	3	mouse	inhalation	NTP (US)	2007	NTP (US)	1999	x	
98-85-1	alpha-Methylbenzyl alcohol	3	mouse	gavage	NTP (US)	1990	NTP (US)	1990		x
98-85-1	alpha-Methylbenzyl alcohol	3	rat	gavage	NTP (US)	1990	NTP (US)	1990	x	
98-95-3	Nitrobenzene	3	mouse	inhalation	BUA Report	1991	Cattley RC, et al.	1994	x	
98-95-3	Nitrobenzene	3	rat	inhalation	BUA Report	1991	Cattley RC, et al.	1994	x	
98-95-3	Nitrobenzene	3	rat	inhalation	BUA Report	1991	Cattley RC, et al.	1994		x
98-95-3	Nitrobenzene	3	rat	inhalation	BUA Report	1991	Cattley RC, et al.	1994	x	
100-41-4	Ethylbenzene	3	mouse	inhalation	NTP (US)	1992	Brown WR	2000	x	
100-41-4	Ethylbenzene	3	rat	inhalation	Hard GC 2000 NTP (US) 1992	2000	Chan PC 1998 Hard GC 2000	1998	x	
100-41-4	Ethylbenzene	1	rat	inhalation	Cragg et al.	1989	Hard GC	2000	x	x
100-41-4	Ethylbenzene	2	rat	inhalation	Cragg et al.	1989	NTP (US)	1999	x	
100-41-4	Ethylbenzene	1	mouse	inhalation	Cragg et al.	1989	NTP (US)	1992	x	
100-41-4	Ethylbenzene	2	mouse	inhalation	Cragg et al.	1989	NTP (US)	1999	x	
100-42-5	Styrene	3	mouse	inhalation	Cruzan, G et al.	1997	Cruzan, G et al.	2001	x	
100-42-5	Styrene	3	rat	inhalation	Cruzan, G et al.	1997	Cruzan, G et al.	1998		x
100-42-5	Styrene	3	rat	inhalation	Cruzan, G et al.	1997	Cruzan, G et al.	1998	x	
100-42-5	Styrene	2	rat	inhalation	Loquet, G et al.	1999	Cruzan, G et al.	1998	x	
100-42-5	Styrene	1	rat	inhalation	Loquet, G et al.	1999	Cruzan, G et al.	1997	x	
100-52-7	Benzaldehyde	3	mouse	gavage	NTP (US)	1990	NTP (US)	1990	x	x
100-52-7	Benzaldehyde	3	mouse	gavage	NTP (US)	1990	NTP (US)	1990	x	

100-52-7	Benzaldehyde	3	rat	gavage	NTP (US)	1990	NTP (US)	1990	x	
101-80-4	4,4´-Diaminodiphenyl ether	3	rat	feed	NCI (National Cancer Institute)	1980	NCI (National Cancer Institute)	1980	x	
101-80-4	4,4´-Diaminodiphenyl ether	3	mouse	feed	NCI (Nat. Cancer Inst.),	1980	NCI (National Cancer Institute)	1980	x	
103-23-1	Di(2-ethylhexyl) adipate	3	mouse	feed	Lake, BG et al.	1997	NTP (US) Kluwe, WM	1982 1985	x	
103-23-1	Di(2-ethylhexyl) adipate	3	rat	feed	Lake, BG et al.	1997	NTP (US) Kluwe, WM	1982 1985	x	
105-60-2	Caprolactam	3	rat	feed	TNO	1971	NTP (US)	1982	x	
105-60-2	Caprolactam	3	rat	feed	TNO	1970	NTP (US)	1982	x	
106-46-7	p-Dichlorobenzene	3	mouse	gavage	NTP (US)	1987	NTP (US)	1987	x	
106-46-7	p-Dichlorobenzene	3	rat	gavage	NTP (US)	1987	NTP (US)	1987	x	
106-47-8	p-Chloroaniline	3	mouse	gavage	NTP (US)	1989	NTP (US)	1989	x	
106-47-8	p-Chloroaniline	3	rat	gavage	NTP (US)	1989	NTP (US)	1989	x	
106-47-8	p-Chloroaniline	3	rat	gavage	NTP (US)	1989	NTP (US)	1989		x
106-88-7	Epoxybutane	3	rat	inhalation	NTP (US)	1988	NTP (US)	1988	x	
106-88-7	Epoxybutane	3	mouse	inhalation	NTP (US)	1988	NTP (US)	1988	x	
106-89-8	Epichlorohydrin	2	rat	inhalation	Laskin, S et al.	1980	Laskin, S et al.	1980	x	
106-89-8	Epichlorohydrin	1	rat	inhalation	Laskin, S et al.	1980	Quast, JF et al.	1979	x	
106-89-8	Epichlorohydrin	3	rat	gavage	Daniel, FB	1996	Wester, PW et al.	1985	x	
106-89-8	Epichlorohydrin	2	rat	gavage	Toth, GP et al.	1989	Wester, PW et al.	1985	x	
106-89-8	Epichlorohydrin	1	rat	gavage	Toth, GP et al.	1989	Daniel, FB	1996	x	
106-89-8	Epichlorohydrin	3	rat	inhalation	Quast, JF et al.	1979	Laskin, S et al.	1980	x	
106-92-3	Allyl glycidyl ether	3	rat	inhalation	NTP (US)	1990	NTP (US)	1990	x	
106-92-3	Allyl glycidyl ether	3	mouse	inhalation	NTP (US)	1990	NTP (US)	1990	x	
106-93-4	1,2-Dibromoethane	3	mouse	inhalation	Reznik, G et al.	1980	NTP (US)	1982	x	
106-93-4	1,2-	3	rat	inhalation	Reznik, G	1980	NTP (US)	1982	x	

	Dibromoethane										
106-94-5	1-Bromopropane	1	rat	inhalation	ClinTrials	1997	Clin. Trials	1997	x		
106-94-5	1-Bromopropane	1	rat	inhalation	ClinTrials	1997	Ichihara G. et al.	2000	x		
106-94-5	1-Bromopropane	1	rat	inhalation	ClinTrials	1997	Ichihara G. et al.	2000		x	
107-02-8	Acrolein	1	rat	inhalation	Leach, CL, et al	1987	Feron, VJ, et al.	1978	x		
107-02-8	Acrolein	3	rat	gavage	NTP (US)	2006	Parent, RA, et al.	1992	x		
107-13-1	Acrylonitrile	3	mouse	gavage	NTP (US) NTP (US)	2001 2006	NTP (US) NTP (US)	2001 2006	x		
107-13-1	Acrylonitrile	3	mouse	gavage	NTP (US) NTP (US)	2001 2006	NTP (US) NTP (US)	2001 2006		x	
107-15-3	Ethylenediamine	3	rat	feed	Yang, R, et al. Dow,	1983 1982	Yang, R, et al. Union Carbide, Bushy Run Res Center	1984 1991	x		
107-15-3	Ethylenediamine	3	rat	feed	Yang, R, et al. Dow,	1983 1982	Yang, R, et al. Union Carbide, Bushy Run Res Center	1984 1991		x	
107-21-1	Ethylene glycol	3	mouse	feed	Melnick, RL,	1984	NTP (US)	1993	x		
107-21-1	Ethylene glycol	3	mouse	feed	Melnick, RL,	1984	NTP (US)	1993	x		
107-21-1	Ethylene glycol	3	rat	feed	Melnick, RL,	1984	DePass, LR, et al.	1986	x	x	s
107-98-2	2-Propylene glycol 1-methyl ether	3	rat	inhalation	Landry TD et al.	1983	Spencer P J et al.	2002	x	x	
107-98-2	2-Propylene glycol 1-methyl ether	3	mouse	inhalation	Spencer P J et al.	2002	Spencer P J et al.	2002	x		
108-31-6	Maleic anhydride	3	rat	feed	Humiston et al.	1975	CIIT Research Triangle Park	1983	x		
108-46-3	Resorcinol	3	rat	gavage	NTP (US)	1992	NTP (US)	1992	x		
108-46-3	Resorcinol	3	mouse	gavage	NTP (US)	1992	NTP (US)	1992	x		
108-78-1	Melamine	3	rat	feed	NTP (US) Melnick, RL et al.	1983	NTP (US) Melnick, RL et al.	1983 1984	x		
108-78-1	Melamine	3	mouse	feed	NTP (US) Melnick, RL et al.	1983 1984	NTP (US) Melnick, RL et al.	1983 1984	x		
109-69-3	1-Chlorobutane	3	rat	gavage	NTP (US)	1986	NTP (US)	1986	x		
109-86-4	Ethylene glycol	1	rat	drinking	Exon JH et al.	1991	NTP (US)	1993	x		

	monomethyl ether			water							
109-86-4	Ethylene glycol monomethyl ether	1	rat	drinking water	Exon JH et al.	1991	NTP (US)	1993	x		
109-99-9	Tetrahydrofuran	3	rat	inhalation	NTP (US)	1998	NTP (US)	1998	x		
109-99-9	Tetrahydrofuran	3	mouse	inhalation	NTP (US)	1998	NTP (US)	1998	x		
110-00-9	Furan	3	rat	gavage	NTP (US)	1993	NTP (US)	1993	x		
110-00-9	Furan	3	rat	gavage	NTP (US)	1993	NTP (US)	1993		x	
110-00-9	Furan	3	mouse	gavage	NTP (US)	1993	NTP (US)	1993	x		
110-86-1	Pyridine	3	rat	drinking water	NTP (US)	2000	NTP (US)	2000	x		
110-86-1	Pyridine	3	rat	drinking water	NTP (US)	2000	NTP (US)	2000	x		
110-86-1	Pyridine	3	mouse	drinking water	NTP (US)	2000	NTP (US)	2000	x		
110-86-1	Pyridine	3	mouse	drinking water	NTP (US)	2000	NTP (US)	2000	x		
110-86-1	Pyridine	3	rat	drinking water	NTP (US)	2000	NTP (US)	2000	x		
110-86-1	Pyridine	3	rat	drinking water	NTP (US)	2000	NTP (US)	2000		x	
110-86-1	Pyridine	3	rat	drinking water	NTP (US)	2000	NTP (US)	2000	x		
111-30-8	Glutaraldehyde	3	mouse	inhalation	NTP (US)	1993	NTP (US)	1999	x		
111-48-8	Thiodiglycol	1	rat	gavage	BASF AG	1993	Angerhofer RA et al.	1997	x	x	s
111-76-2	Ethylene glycol (mono) n-butyl ether	3	rat	inhalation	Dodd, DE, et al.	1983	NTP (US)	2000	x		
111-76-2	Ethylene glycol (mono) n-butyl ether	3	rat	inhalation	NTP (US)	2000	NTP (US)	2000	x		
111-76-2	Ethylene glycol (mono) n-butyl ether	3	mouse	inhalation	NTP (US)	2000	NTP (US)	2000	x		
111-76-2	Ethylene glycol (mono) n-butyl	1	rat	drinking water	Exon JH et al.	1991	NTP (US)	1993	x		

	ether										
111-76-2	Ethylene glycol (mono) n-butyl ether	1	rat	drinking water	Exon JH et al.	1991	NTP (US)	1993	x		
111-76-2	Ethylene glycol (mono) n-butyl ether	3	rat	inhalation	NTP (US)	2000	NTP (US)	2000		x	
115-07-1	Propylene	3	rat	inhalation	NTP (US)	1985	Ciliberti A et al.	1988	x		
115-07-1	Propylene	3	rat	inhalation	NTP (US)	1985	NTP (US)	1985	x		
115-10-6	Dimethyl ether	3	rat	inhalation	Reutzel, PG, et al. Reutzel, PG & Woutersen, RA	1981	Du Pont de Nemours, Haskell Lab. Tox. Industr. Med.	1986	x	x	
115-11-7	Isobutylene	3	mouse	inhalation	NTP (US)	1998	NTP (US)	1998	x		
115-11-7	Isobutylene	3	rat	inhalation	NTP (US)	1998	NTP (US)	1998	x		
115-29-7	Endosulfan	3	mouse	feed	Barnard et al.	1984	Donaubauer	1988	x	x	p
115-29-7	Endosulfan	1	rat	feed	Leist and Kramer	1985	Barnard et al.	1985	x		
115-29-7	Endosulfan	2	rat	feed	Leist and Kramer	1985	Ruckman et al.	1988	x		
115-29-7	Endosulfan	3	rat	feed	Barnard et al.	1985	Ruckman et al.	1988	x		
115-32-2	2,2,2-trichloro-1,1-di(4-chlorophenyl) ethanol	3	rat	feed	Goldman et al.	1986	Larson	1957	x		
115-32-2	2,2,2-trichloro-1,1-di(4-chlorophenyl) ethanol	3	rat	feed	Goldman et al.	1986	Hazelton and Harris	1989	x	x	p
115-32-2	2,2,2-trichloro-1,1-di(4-chlorophenyl) ethanol	3	rat	feed	Verschuuren et al.	1973	Larson	1957	x		
115-32-2	2,2,2-trichloro-1,1-di(4-chlorophenyl) ethanol	3	rat	feed	Verschuuren et al.	1973	Hazelton and Harris	1989	x		
115-32-2	2,2,2-trichloro-1,1-di(4-chlorophenyl)	3	rat	feed	Smith et al.	1959	Larson	1957	x		

	ethanol										
115-32-2	2,2,2-trichloro-1,1-di(4-chlorophenyl) ethanol	3	rat	feed	Smith et al.	1959	Hazelton and Harris	1989	x		
116-06-3	2-methyl-2-(methylthio)propri onaldehyde o-methylcarbomylo xime	3	rat	feed	Weil and Carpenter	1963	Weil and Carpenter	1965	x	x	p
116-06-3	2-methyl-2-(methylthio)propri onaldehyde o-methylcarbomylo xime	3	rat	feed	Weil and Carpenter	1963	NIH	1979	x		
116-14-3	Tetrafluoroethyle ne	3	rat	inhalation	NTP	1997	NTP (US)	1997	x	x	
119-61-9	Benzophenone	3	mouse	feed	NTP (US)	2000	NTP (US)	2006	x		
119-61-9	Benzophenone	3	rat	feed	NTP (US)	2000	NTP (US)	2006	x		
120-82-1	1,2,4-Trichlorobenzene	3	rat	feed	Côté et al.	1988	Standard Chlorine of Delaware, Hazelton Washington	1994	x	x	
120-82-1	1,2,4-Trichlorobenzene	3	rat	feed	Côté et al.	1988	Standard Chlorine of Delaware, Hazelton Washington	1994	x		
120-83-2	2,4-Dichlorophenol	3	mouse	feed	NTP (US)	1989	NTP (US)	1989	x		
120-83-2	2,4-Dichlorophenol	3	rat	feed	NTP (US)	1989	NTP (US)	1989	x		
120-83-2	2,4-Dichlorophenol	3	rat	feed	NTP (US)	1989	NTP (US)	1989		x	
120-83-2	2,4-Dichlorophenol	3	rat	feed	NTP (US)	1989	NTP (US)	1989	x		
121-69-7	N,N-Dimethylaniline	3	rat	gavage	NTP (US National Toxicology Programm)	1989	NTP (US National Toxicology Programm)	1989	x		
121-69-7	N,N-Dimethylaniline	3	mouse	gavage	NTP (US National Toxicology Programm)	1989	NTP (US National Toxicology Programm)	1989	x		
121-79-9	Propyl gallate	1	rat	feed	Strik, JTWA et al.	1986	Speijers, GJA et al.	1993	x	x	

121-79-9	Propyl gallate	2	rat	feed	Strik, JTWA et al.	1986	Abdo, KM et al.	1983	x		
121-79-9	Propyl gallate	3	rat	feed	Speijers, GJA et al.	1993	Abdo, KM et al.	1983	x		
122-99-6	Ethylene glycol (mono) phenyl ether	1	rat	feed	Unilever	1991	Unilever	1991	x	x	s
123-31-9	Hydroquinone	3	rat	gavage	NTP (US) Kari, FW, et al.	1989 1992	NTP (US) Kari, FW, et al.	1989 1992	x		
123-31-9	Hydroquinone	3	rat	gavage	NTP (US) Kari, FW, et al.	1989 1992	NTP (US) Kari, FW, et al.	1989 1992		x	
123-31-9	Hydroquinone	3	mouse	gavage	NTP (US)	1989	Kari, FW, et al. NTP (US)	1992 1989	x		
123-91-1	1,4-Dioxane	3	rat	drinking water	Japan Bioassay Research Center	1998	Kociba	1974	x		
123-91-1	1,4-Dioxane	3	rat	drinking water	Japan Bioassay Research Center	1998	Yamazaki K	1994	x		
123-91-1	1,4-Dioxane	3	rat	drinking water	Japan Bioassay Research Center	1998	Yamazaki K	1994		x	
123-91-1	1,4-Dioxane	3	rat	drinking water	Japan Bioassay Research Center	1998	NCI	1978	x		
123-91-1	1,4-Dioxane	3	mouse	drinking water	Japan Bioassay Research Center	1998	Yamazaki K	1994	x		
126-73-8	Tributyl phosphate	3	rat	feed	Cascieri, T et al. 1985 FMC Corporation, Toxicology Laboratory 1985	1985	Auletta, CS et al. 1998 Pharmaco LSR Inc. 1994	1998	x	x	p
126-99-8	Chloroprene	3	rat	inhalation	Melnick RL et al. NTP (US)	1996 1998	NTP (US)	1998	x		
126-99-8	Chloroprene	3	mouse	inhalation	NTP (US)	1998	NTP (US)	1998	x		
127-18-4	Tetrachloroethene	3	rat	inhalation	NTP (US)	1986	NTP (US)	1986	x		
127-18-4	Tetrachloroethene	3	mouse	inhalation	NTP (US)	1986	NTP (US)	1986	x		
127-18-4	Tetrachloroethene	1	rat	inhalation	Odum J et al.	1988	NTP (US)	1986	x		
127-18-4	Tetrachloroethene	2	rat	inhalation	Odum J et al.	1988	NTP (US)	1986	x		
127-18-4	Tetrachloroethen	1	mouse	inhalation	Odum J et al.	1988	NTP (US)	1986	x		

	e										
127-18-4	Tetrachloroethene	2	mouse	inhalation	Odum J et al.	1988	NTP (US)	1986	x		
131-17-9	Diallyl phtalate	3	rat	gavage	NTP (US)	1985	NTP (US)	1985	x		
131-17-9	Diallyl phtalate	3	rat	gavage	NTP (US)	1985	NTP (US)	1985		x	
135-88-6	N-Phenyl-2-naphthylamine	3	rat	feed	NTP (US)	1988	NTP (US)	1988	x		
135-88-6	N-Phenyl-2-naphthylamine	3	mouse	feed	NTP (US)	1988	NTP (US)	1988	x		
135-88-6	N-Phenyl-2-naphthylamine	3	mouse	feed	NTP (US)	1988	NTP (US)	1988		x	
136-77-6	4-Hexylresorcinol	3	rat	gavage	NTP (US)	1988	NTP (US)	1998	x		
136-77-6	4-Hexylresorcinol	3	rat	gavage	NTP (US)	1988	NTP (US)	1998		x	
136-77-6	4-Hexylresorcinol	3	mouse	gavage	NTP (US)	1998	NTP (US)	1998	x		
140-11-4	Benzyl acetate	3	mouse	feed	NTP (US)	1993	NTP (US)	1993	x		
140-11-4	Benzyl acetate	3	rat	feed	NTP (US)	1993	Longnecker	1990	x		
140-11-4	Benzyl acetate	3	rat	feed	NTP (US)	1993	NTP (US)	1993	x	x	
140-88-5	Ethyl acrylate	3	rat	gavage	NTP (National Toxicology Program)	1986	NTP (US)	1986	x		
271-89-6	Benzofuran	3	mouse	gavage	NTP (US)	1989	NTP (US)	1989	x		
271-89-6	Benzofuran	3	rat	gavage	NTP (US)	1989	NTP (US)	1989	x		
288-32-4	Imidazol	1	rat	gavage	BASF AG	1976	BASF AG	2002	x	x	
298-00-0	Parathion-Methyl	3	rat	feed	Daly	1980	Eiben	1987	x		
298-00-0	Parathion-Methyl	3	rat	feed	Daly	1980	Daly	1984	x	x	p
298-04-4	Disulfoton	1	rat	inhalation	Thyssen	1980	Shiotsuka	1989	x		
298-04-4	Disulfoton	1	rat	inhalation	Thyssen	1980	Shiotsuka	1989	x	x	
298-04-4	Disulfoton	1	rat	inhalation	Shiotsuka	1988	Shiotsuka	1989	x		
298-04-4	Disulfoton	3	rat	feed	Motzsche	1972	Carpy and Klotzsche	1975	x		
298-04-4	Disulfoton	3	rat	feed	Motzsche	1972	Hayes	1985	x	x	p
302-17-0	Chloral hydrate	3	mouse	drinking water	Sanders, VM et al.	1982	George, MH et al.	2000	x		
306-83-2	1,1-Dichloro-2,2,2-trifluoroethane	2	rat	inhalation	PAFT, Haskell Laboratory	1989	PAFT, Haskell Laboratory	1991		x	

306-83-2	1,1-Dichloro-2,2,2-trifluoroethane	2	rat	inhalation	PAFT, Haskell Laboratory	1989	PAFT, Haskell Laboratory	1991	x	
306-83-2	1,1-Dichloro-2,2,2-trifluoroethane	1	rat	inhalation	PAFT, Haskell Laboratory	1989	Rusch GM. et al.	1993	x	
306-83-2	1,1-Dichloro-2,2,2-trifluoroethane	2	rat	inhalation	PAFT, Imperial Chemical Industries, Central Toixology Laboratories	1990	PAFT, Haskell Laboratory	1991	x	
306-83-2	1,1-Dichloro-2,2,2-trifluoroethane	1	rat	inhalation	PAFT, Imperial Chemical Industries, Central Toixology Laboratories	1990	Rusch GM. et al.	1993	x	
306-83-2	1,1-Dichloro-2,2,2-trifluoroethane	3	rat	inhalation	Rusch GM. et al.	1993	PAFT, Haskell Laboratory	1991		x
306-83-2	1,1-Dichloro-2,2,2-trifluoroethane	3	rat	inhalation	Rusch GM. et al.	1993	PAFT, Haskell Laboratory	1991	x	
460-73-1	1,1,1,3,3-Pentafluoropropane	1	rat	inhalation	Rusch et al.	1999	Rusch et al.	1999	x	x
492-80-8	Auramine base	3	rat	feed	Kirsch, P. et al.	1978	Kirsch, et al.	1978	x	x
492-80-8	Auramine base	3	rat	feed	Kirsch, P, et al.	1978	Kirsch, et al.	1978	x	
509-14-8	Tetranitromethane	3	mouse	inhalation	NTP (US)	1990	NTP (US) Bucher, JR et al.	1990 1991	x	
509-14-8	Tetranitromethane	3	rat	inhalation	NTP (US)	1990	NTP (US) Bucher, JR et al.	1990 1991	x	
532-27-4	2-Chloroacetophenone	3	rat	inhalation	NTP (US)	1990	NTP (US)	1990	x	
532-27-4	2-Chloroacetophenone	3	mouse	inhalation	NTP (US)	1990	NTP (US)	1990	x	
534-52-1	4,6-Dinitro-o-cresol	1	mouse	feed	Broadmeadow, A	1996	Kelly, J	1995	x	x

534-52-1	4,6-Dinitro-o-cresol	3	rat	feed	den Tonkelaar, EM et al.	1983	Broadmeadow, A	1991	x	
541-41-3	Chloroformic acid ethyl ester	2	rat	inhalation	Gage JC	1970	Sellakumar AR	1987	x	
541-73-1	1,3-Dichlorobenzene	1	rat	gavage	Hoechst AG	1989	Mc Cauley et al.	1995	x	
542-56-3	Isobutyl Nitrite	3	rat	inhalation	NTP (US)	1996	NTP (US)	1996	x	
542-56-3	Isobutyl Nitrite	3	mouse	inhalation	NTP (US)	1996	NTP (US)	1996		x
542-56-3	Isobutyl Nitrite	3	mouse	inhalation	NTP (US)	1996	NTP (US)	1996	x	
556-52-5	Glycidol	3	rat	gavage	NTP (National Toxicology Program)	1990	NTP (US) Irwin, RD et al.	1990 1996	x	
556-52-5	Glycidol	3	mouse	gavage	NTP (National Toxicology Program)	1990	NTP (US) Irwin, RD et al.	1990 1996	x	
599-79-1	Salicylazosulfapyridine	3	rat	gavage	NTP (US)	1997	NTP (US)	1997	x	
599-79-1	Salicylazosulfapyridine	3	mouse	gavage	NTP (US)	1997	NTP (US)	1997	x	
599-79-1	Salicylazosulfapyridine	3	mouse	gavage	NTP (US)	1997	NTP (US)	1997		x
630-20-6	1,1,1,2-Tetrachloroethane	2	rat	gavage	NTP (US)	1996	NTP (US)	1983	x	
630-20-6	1,1,1,2-Tetrachloroethane	1	rat	gavage	NTP (US)	1996	NTP (US)	1983	x	
630-20-6	1,1,1,2-Tetrachloroethane	3	rat	gavage	NTP (US)	1983	NTP (US)	1983	x	
811-97-2	1,1,1,2-Tetrafluoroethane	2	rat	inhalation	ECETOC (European Centre Ecotox. Tox. Chem.),	1995	Collins, MA, et al.	1995	x	x
811-97-2	1,1,1,2-Tetrafluoroethane	1	mouse	inhalation	IPACTI (Int Pharm Aerosol Consortium Tox Test)	1992	IPACTI (Int Pharm Aerosol Consortium Tox Test),	1992		x
811-97-2	1,1,1,2-Tetrafluoroethane	1	mouse	inhalation	IPACTI (Int Pharm Aerosol Consortium Tox Test)	1992	IPACTI (Int Pharm Aerosol Consortium Tox Test),	1992	x	

822-06-0	Heymethylene diisocyanate	1	rat	inhalation	Mobay Chemical	1984	Mobay Chemical	1988	x		
822-06-0	Heymethylene diisocyanate	2	rat	inhalation	Mobay Chemical	1984	Mobay Chemical	1989	x		
822-06-0	Heymethylene diisocyanate	3	rat	inhalation	Mobay Chemical	1988	Mobay Chemical	1989	x		
822-36-6	4-Methylimidazole	3	rat	feed	NTP (US)	2004	NTP (US)	2007	x		
822-36-6	4-Methylimidazole	3	rat	feed	NTP (US)	2004	NTP (US)	2007		x	
822-36-6	4-Methylimidazole	3	mouse	feed	NTP (US)	2004	NTP (US)	2007	x		
836-30-6	4-Nitrodiphenylamine	1	rat	feed	Monsanto	1983	Monsanto	1983	x	x	
868-85-9	Dimethyl hydrogen phosphite	1	rat	gavage	Nomeir, AA Nomeir, AA	1986 1988	NTP (US)	1985	x	x	p
868-85-9	Dimethyl hydrogen phosphite	2	rat	gavage	Nomeir, AA Nomeir, AA	1988 1986	NTP (US)	1985	x	x	p
868-85-9	Dimethyl hydrogen phosphite	3	rat	gavage	NTP (US)	1985	NTP (US)	1985	x	x	p
868-85-9	Dimethyl hydrogen phosphite	3	mouse	gavage	NTP (US)	1985	NTP (US)	1985	x		
872-50-4	N-Methyl-2-pyrrolidone	2	rat	inhalation	Lee, KP, et al.	1987	Lee, KP, et al.	1987	x		
872-50-4	N-Methyl-2-pyrrolidone	1	rat	inhalation	Lee, KP, et al.	1987	BASF	1994	x		
872-50-4	N-Methyl-2-pyrrolidone	3	rat	inhalation	BASF	1994	Lee, KP, et al.	1987		x	
872-50-4	N-Methyl-2-pyrrolidone	3	rat	inhalation	BASF	1994	Lee, KP, et al.	1987	x		
999-81-5	Chlormequat	2	rat	feed	Schilling et al.	1990	NCI	1979	x		
1241-94-7	Diphenyl-2-ethylhexyl	1	rat	feed	BIBRA Toxicology International,	1990	BIBRA Toxicology International, Carshalton,	1992	x		

	phosphate				Carshalton, UK		UK			
1241-94-7	Diphenyl-2-ethylhexyl phosphate	1	rat	feed	BIBRA Toxicology International, Carshalton, UK	1990	BIBRA Toxicology International, Carshalton, UK	1992	x	x p
1490-04-6	Menthol	3	mouse	feed	Tracor Jitco	1976	NCI	1979	x	
1490-04-6	Menthol	1	rat	gavage	Thorup I	1983	Haarmann & Reimer	1974	x	x
1634-04-4	Methyl-tertiary-butyl ether	1	rat	gavage	IITRI,	1992	Zhou and Ye	1999	x	
1634-04-4	Methyl-tertiary-butyl ether	1	rat	gavage	IITRI,	1992	Zhou and Ye	1999		x
1634-04-4	Methyl-tertiary-butyl ether	2	rat	gavage	IITRI,	1992	Belpoggi	1995	x	
1634-04-4	Methyl-tertiary-butyl ether	1	rat	inhalation	Chun	1993	Greenough	1980	x	x
1634-04-4	Methyl-tertiary-butyl ether	1	rat	inhalation	Chun	1993	Daughtrey Lington Dodd	1997 1997 1989	x	
1634-04-4	Methyl-tertiary-butyl ether	2	rat	inhalation	Chun	1993	Bird	1997	x	x
1634-04-4	Methyl-tertiary-butyl ether	3	rat	inhalation	Greenough	1980	Bird	1997	x	x
1634-04-4	Methyl-tertiary-butyl ether	3	rat	inhalation	Daughtrey Lington Dodd	1997 1997 1989	Bird	1997	x	
1634-04-4	Methyl-tertiary-butyl ether	3	rat	gavage	Zhou and Ye	1999	Belpoggi	1995	x	
1717-00-6	1,1-Dichloro-1-fluoroethane	3	rat	inhalation	Brock RJ et al. Landry TD et al.	1995 1989	HARDY CJ MillischerR-J et al.	1993 1995	x	x
1847-58-1	Sodium Lauryl Sulfoacetate	1	rat	gavage	N.N., J. American College of Toxicology	1987	N.N., J. American College of Toxicology	1987	x	x s
1948-33-0	tert-Butylhydroquinone	3	rat	feed	NTP (US)	1995	NTP (US)	1995	x	
1948-33-0	tert-Butylhydroquinone	1	rat	feed	Altmann, H-J et al.	1985	NTP (US)	1995	x	
1948-33-0	tert-	2	rat	feed	Altmann, H-J et al.	1985	NTP (US)	1995	x	

	Butylhydroquinone									
1948-33-0	tert-Butylhydroquinone	3	mouse	feed	NTP (US)	1995	NTP (US)	1995	x	
1948-33-0	tert-Butylhydroquinone	3	mouse	feed	NTP (US)	1995	NTP (US)	1995		x
2238-07-5	Diglycidyl ether	1	rat	inhalation	authors not given		authors not given		x	
2431-50-7	2,3,4-Trichloro-1-butene	3	rat	inhalation	Reuzel, PGJ & Dreef-van der Meulen, HC	1978	Reuzel, PGJ et al.	1981	x	
2431-50-7	2,3,4-Trichloro-1-butene	3	rat	inhalation	Reuzel, PGJ & Dreef-van der Meulen, HC	1978	Reuzel, PGJ et al.	1981		x
2431-50-7	2,3,4-Trichloro-1-butene	2	rat	inhalation	Reuzel, PGJ et al.	1976	Reuzel, PGJ et al.	1981	x	
2431-50-7	2,3,4-Trichloro-1-butene	2	rat	inhalation	Reuzel, PGJ et al.	1976	Reuzel, PGJ et al.	1981		x
2431-50-7	2,3,4-Trichloro-1-butene	1	rat	inhalation	Reuzel, PGJ et al.	1976	Reuzel, PGJ & Dreef-van der Meulen, HC	1978	x	
2431-50-7	2,3,4-Trichloro-1-butene	1	rat	inhalation	Reuzel, PGJ et al.	1976	Reuzel, PGJ & Dreef-van der Meulen, HC	1978		x
2432-99-7	11-Aminoundecanoic acid	3	rat	feed	NTP (US)	1982	Dunnick JK et al. NTP (US) NTP (US)	1983 1982 2004	x	
2432-99-7	11-Aminoundecanoic acid	1	rat	feed	Atofina	2001	NTP (US)	1982	x	x s
2432-99-7	11-Aminoundecanoic acid	2	rat	feed	Atofina	2001	NTP (US) NTP (US) Dunnick JK et al.	2004 1982 1983	x	
2432-99-7	11-Aminoundecanoic acid	3	mouse	feed	NTP (US)	1982	Dunnick et al. NTP (US) NTP (US)	1983 1982 2004	x	
2698-41-1	o-Chlorobenzalmalonitrile	3	rat	inhalation	NTP (US)	1990	NTP (US)	1990	x	
2698-41-1	o-	3	rat	inhalation	NTP (US)	1990	NTP (US)	1990		x

	Chlorobenzalmalonitrile										
2698-41-1	o-Chlorobenzalmalonitrile	3	mouse	inhalation	NTP (US)	1990	NTP (US)	1990	x		
2835-39-4	Allyl isovalerate	3	rat	gavage	NTP (US)	1983	NTP (US)	1983	x	x	
2835-39-4	Allyl isovalerate	3	mouse	gavage	NTP (US)	1983	NTP (US)	1983	x		
3347-22-6	Dithianon	3	rat	feed	Leuschner and Neumann	1987	Wheldon et al. Spicer and Benson	1969 1971	x		
3347-22-6	Dithianon	3	rat	feed	Leuschner and Neumann	1987	Brown	1991	x	x	p
4180-23-8	trans-Anethole	3	rat	feed	Minnema, DJ Newberne	1997 1997	Truhaut, R et al.	1989	x		
4180-23-8	trans-Anethole	2	rat	feed	Newberne, PM Minnema, DJ	1997 1997	Truhaut, R et al.	1989	x		
4180-23-8	trans-Anethole	1	rat	feed	Minnema, DJ Newberne, PM	1997 1997	Minnema, DJ	1997	x	x	
5392-40-5	Citral	3	rat	feed	NTP (US)	2003	NTP (US)	2003	x		
5392-40-5	Citral	3	rat	feed	NTP (US)	2003	NTP (US)	2003	x		
5392-40-5	Citral	3	mouse	feed	NTP (US)	2003	NTP (US)	2001	x		
5989-27-5	d-Limonene	1	rat	gavage	Tsuji, M et al.	1975	Webb, DR et al.	1989	x		
5989-27-5	d-Limonene	2	rat	gavage	Tsuji, M et al.	1975	NTP (US)	1990	x		
5989-27-5	d-Limonene	1	rat	gavage	Tsuji, M et al.	1975	NTP (National Toxicology Programm)	1990	x		
5989-27-5	d-Limonene	1	rat	gavage	Kanerva, RL et al.	1987	Webb, DR et al.	1989	x	x	
5989-27-5	d-Limonene	2	rat	gavage	Kanerva, RL et al.	1987	NTP (US)	1990	x		
5989-27-5	d-Limonene	1	rat	gavage	Kanerva, RL et al.	1987	NTP (National Toxicology Programm)	1990	x		
5989-27-5	d-Limonene	3	rat	gavage	Webb, DR et al.	1989	NTP (US)	1990	x		
5989-27-5	d-Limonene	3	rat	gavage	NTP (National Toxicology Programm)	1990	NTP (US)	1990	x		
5989-27-5	d-Limonene	3	mouse	gavage	NTP (National Toxicology Programm)	1990	NTP (US)	1990	x	x	
6923-22-4	Dimethyl-1-methyl-2-methyl-carbamoyl-vinyl	3	rat	feed	Shellenberger and Newell	1964	Johnston et al.	1967	x		

	phosphate										
7414-83-7	Etidronate Disodium	3	rat	feed	Nixon et al.	1972	confidential		x		
7414-83-7	Etidronate Disodium	1	rat	feed	confidential		Nixon et al.	1972	x		
9004-82-4	NaC12-15AE3S	1	rat	feed	confidential		Walker AIT	1967	x		
9004-82-4	NaC12-15AE3S	1	rat	feed	confidential		Walker AIT	1967		x	s
10016-20-3	alpha-Cyclodextrin	1	rat	feed	Lina, BAR & Bruyntjes, JP	1987	Lina, BAR	1992	x	x	
10265-92-6	Methamidophos	1	rat	inhalation	Paulhuhn	1987	Paulhuhn	1988	x	x	
13071-79-9	Terbufos	1	rat	feed	Morici	1972	Daly	1979	x		
13071-79-9	Terbufos	1	rat	feed	Morici	1972	Daly	1979		x	p
13071-79-9	Terbufos	2	rat	feed	Morici	1972	Rapp	1974	x	x	p
13071-79-9	Terbufos	3	rat	feed	Daly	1979	McConnell	1983	x		
13071-79-9	Terbufos	3	rat	feed	Daly	1979	McConnell	1983		x	p
14371-10-9	trans-Cinnamaldehyde	3	rat	feed	NTP (US) NTP (US)	2004 2006	NTP (US) NTP (US)	2004 2006	x		
14371-10-9	trans-Cinnamaldehyde	3	mouse	feed	NTP (US) 2004 NTP (US) 2006	2004	NTP (US) 2004 NTP (US) 2006	2004	x		
16752-77-5	S-methyl-N-[(methyl carbomyl)oxy] thioacetimidate	3	rat	feed	Paynter	1966	Kaplan et al.	1981	x	x	p
17804-35-2	Benomyl	3	rat	feed	Sherman et al.	1967	Sherman Lee	1969 1977	x		
18181-80-1	Bromopropylate	3	rat	feed	Paterson and Drake	1967	Basler W. et al.	1989	x		
18181-80-1	Bromopropylate	3	rat	feed	Paterson and Drake	1967	Basler W. et al.	1989		x	
18181-80-1	Bromopropylate	3	rat	feed	Paterson and Drake	1967	Coulston et al.	1970	x		
23135-22-0	N,N-dimethyl-2-methylcarbomoyl oxyimino 2-(methylthio)acetamide	3	rat	feed	Snee et al.	1969	Sherman et al.	1972	x		
23135-22-0	N,N-dimethyl-2-methylcarbomoyl	3	rat	feed	Snee et al.	1969	Sherman et al.	1972		x	p

	oxyimino 2-(methylthio)acetamide										
24017-47-8	Triazophos	3	rat	feed	Tennekes et al.	1986	Tennekes et al.	1990	x		
24017-47-8	Triazophos	3	rat	feed	Tennekes et al.	1986	Tennekes et al.	1990		x	p
24017-47-8	Triazophos	3	rat	feed	Tennekes et al.	1986	JMPR	1991	x		
24017-47-8	Triazophos	3	rat	feed	Til et al.	1971	Tennekes et al.	1990	x		
24017-47-8	Triazophos	3	rat	feed	Til et al.	1971	JMPR	1991	x		
25057-89-0	Bentazone	3	rat	feed	Tennekes et al.	1987	Takehara et al.	1984	x	x	p
25057-89-0	Bentazone	3	rat	feed	JMPR (Part II Toxikology)	1991	Takehara et al.	1984	x		
25311-71-1	O-ethyl-0-2-isopropoxy-carbonyl phenyl isopropylphospho r-amidothioate	1	rat	feed	Löser	1978	Löser Urwin and Newman	1973 1973	x	x	p
26761-40-0	Diisodecylphthalate	1	rat	feed	BASF,	1969	BASF,	1969	x		
26761-40-0	Diisodecylphthalate	1	rat	feed	BASF,	1969	BASF,	1969		x	
26761-40-0	Diisodecylphthalate	1	rat	feed	BASF,	1969	Hazleton Laboratories	1968	x		
30025-38-8	Dipropylene glycol monoethyl ether	1	rat	gavage	BP Chemicals, UK	1990	BP Chemicals, UK	2001	x	x	s
33089-61-1	N-methylbis(2,4-xylyliminomethyl) amine	3	rat	feed	Sutton and Williams	1971	Sutton and Offer	1973	x		
38260-54-7	O-6-ethoxy-2-ethyl-pyrimidin-4-yl O,O-dimethyl phosphorothioate	1	rat	feed	Carpy and Klotzsche	1975	Carpy and Klotzsche	1975	x		
38260-54-7	O-6-ethoxy-2-ethyl-pyrimidin-4-yl O,O-dimethyl phosphorothioate	1	rat	feed	Carpy and Klotzsche	1975	Carpy and Klotzsche	1975		x	p
38260-54-7	O-6-ethoxy-2-	2	rat	feed	Carpy and Klotzsche	1975	Carpy and Klotzsche	1976	x		

	ethyl-pyrimidin-4-yl O,O-dimethyl phosphorothioate										
38260-54-7	O-6-ethoxy-2-ethyl-pyrimidin-4-yl O,O-dimethyl phosphorothioate	2	rat	feed	Carpy and Klotzsche	1975	Carpy and Klotzsche	1976		x	p
38260-54-7	O-6-ethoxy-2-ethyl-pyrimidin-4-yl O,O-dimethyl phosphorothioate	3	rat	feed	Carpy and Klotzsche	1975	Carpy and Klotzsche	1976	x		
38260-54-7	O-6-ethoxy-2-ethyl-pyrimidin-4-yl O,O-dimethyl phosphorothioate	3	rat	feed	Carpy and Klotzsche	1975	Carpy and Klotzsche	1976		x	p
39515-41-8	Fenpropathrin	2	mouse	feed	Colley at al.	1981	Colley et al.	1985 1987	x	x	p
39515-41-8	Fenpropathrin	3	rat	feed	Hend and Butterworth	1975	Hend and Gellatly Okuno Aitken and Rushdon	1979	x		
39515-41-8	Fenpropathrin	3	rat	feed	Hend and Butterworth	1976	Hend and Gellatly Okuno Aitken and Rushdon	1979	x		
39515-41-8	Fenpropathrin	3	rat	feed	Yoshida et al.	1986	Hend and Gellatly Okuno Aitken and Rushdon	1979	x	x	p
39515-41-8	Fenpropathrin	3	rat	feed	Yoshida et al.	1986	Warren et al. Fish et al. Dean et al.	1986 1986 1987	x		
39515-42-1	Fenpropathrin	3	rat	feed	Hend and Butterworth	1976	Warren et al. Fish et al. Dean et al.	1986 1986 1987	x		
39515-42-4	Fenpropathrin	3	rat	feed	Hend and Butterworth	1975	Warren et al. Fish et al. Dean et al.	1986 1986 1987	x		
41198-08-7	Profenofos	3	rat	feed	JMPR	1990	JMPR	1990	x		

50471-44-8	Vinclozolin	3	mouse	feed	Schilling et al.	1990	Leuschner et al.	1977	x		
50471-44-8	Vinclozolin	3	mouse	feed	Schilling et al.	1990	Leuschner et al.	1977	x		
50471-44-8	Vinclozolin	3	rat	feed	Hofmann	1974	Leuschner et al.	1977	x		
50471-44-8	Vinclozolin	3	rat	feed	Hofmann	1974	Mellert et al.	1994	x		
50471-44-8	Vinclozolin	3	rat	feed	Hofmann	1974	Mellert et al.	1993	x		
50471-44-8	Vinclozolin	3	rat	feed	Hofmann	1974	Mellert et al.	1994	x		
50471-44-8	Vinclozolin	1	rat	feed	Hoffmann and Munk	1975	Hofmann	1974	x		
50471-44-8	Vinclozolin	1	rat	feed	Hoffmann and Munk	1975	Mellert et al.	1993	x		
50471-44-8	Vinclozolin	1	rat	feed	Hoffmann and Munk	1975	Mellert et al.	1993		x	p
50471-44-8	Vinclozolin	2	rat	feed	Hoffmann and Munk	1975	Leuschner et al.	1977	x		
50471-44-8	Vinclozolin	2	rat	feed	Hoffmann and Munk	1975	Mellert et al.	1994	x		
50471-44-8	Vinclozolin	2	rat	feed	Hoffmann and Munk	1975	Mellert et al.	1994	x		
50471-44-8	Vinclozolin	3	rat	feed	Leuschner et al.	1975	Leuschner et al.	1977	x		
50471-44-8	Vinclozolin	3	rat	feed	Leuschner et al.	1975	Mellert et al.	1993	x		
50471-44-8	Vinclozolin	3	rat	feed	Mellert et al.	1993	Leuschner et al.	1977	x		
50471-44-8	Vinclozolin	3	rat	feed	Mellert et al.	1993	Mellert et al.	1994	x		
50471-44-8	Vinclozolin	3	rat	feed	Mellert et al.	1993	Mellert et al.	1994	x		
50471-44-8	Vinclozolin	3	rat	feed	Mellert et al.	1993	Leuschner et al.	1977	x		
50471-44-8	Vinclozolin	3	rat	feed	Mellert et al.	1993	Mellert et al.	1993	x		
57018-04-9	O,O-Dimethyl O-(2,6-dichloro-4-methylphenyl)phosphorothioate	1	rat	feed	Colley et al.	1982	Kimura et al.	1990	x	x	p
57018-04-9	O,O-Dimethyl O-(2,6-dichloro-4-methylphenyl)phosphorothioate	2	rat	feed	Colley et al.	1982	Pence et al.	1982	x		
57018-04-9	O,O-Dimethyl O-(2,6-dichloro-4-methylphenyl)phosphorothioate	2	rat	feed	Colley et al.	1982	Pence et al.	1982		x	p
57018-04-9	O,O-Dimethyl O-(2,6-dichloro-4-methylphenyl)phosphorothioate	2	rat	feed	Colley et al.	1982	Pence et al. Miyamoto	1985 1985	x		

57018-04-9	O,O-Dimethyl O-(2,6-dichloro-4-methylphenyl)phosphorothioate	3	rat	feed	Kimura et al.	1990	Pence et al.	1982	x		
57018-04-9	O,O-Dimethyl O-(2,6-dichloro-4-methylphenyl)phosphorothioate	3	rat	feed	Kimura et al.	1990	Pence et al. Miyamoto	1985 1985	x	x	p
57018-52-7	Propylene glycol tert-butyl ether	3	rat	inhalation	NTP (US)	2004	NTP (US)	2004	x	x	
57018-52-7	Propylene glycol tert-butyl ether	3	mouse	inhalation	NTP (US)	2004	NTP (US)	2004	x		
60168-88-9	2,4-dichloror-a-(pyramidin-5-yl)benzhydryl alcohol	3	mouse	feed	Hoffman et al.	1975	Hoffman et al.	1978	x	x	p
60168-88-9	2,4-dichloror-a-(pyramidin-5-yl)benzhydryl alcohol	3	rat	feed	Hoffman et al.	1975	Hofmann et al.	1978	x		
60168-88-9	2,4-dichloror-a-(pyramidin-5-yl)benzhydryl alcohol	3	rat	feed	Hoffman et al.	1975	Hofmann et al.	1978	x		
60207-90-1	Propiconazole	3	rat	feed	Sachsse et al.	1979	Hunter et al.	1982	x	x	p
60207-90-1	Propiconazole	2	rat	feed	Basler et al.	1980	Hunter et al.	1982	x	x	p
60207-90-1	Propiconazole	1	rat	feed	Basler et al.	1980	Sachsse et al.	1979	x	x	p
62610-77-9	O-2-methoxycarbonyl prop-1-enyl O,O-dimethyl phsophorothioate	2	rat	feed	Drake	1975	Basler et al.	1980	x	x	p
66215-27-8	N-cyclopropyl-1,3,5-triazine-2,4,6-triamine	3	rat	feed	Goldenthal and Hughes	1979	Blair and Hardisty	1982	x		
66246-88-6	Penconazole	3	mouse	feed	Hiles	1987	JMPR	1992	x		
66246-88-6	Penconazole	1	rat	feed	Basler et al.	1984	Basler et al.	1982	x		

66246-88-6	Penconazole	1	rat	feed	Basler et al.	1984	Basler et al.	1983	x		
66246-88-6	Penconazole	1	rat	feed	Basler et al.	1984	Hiles	1987	x		
66246-88-6	Penconazole	2	rat	feed	Basler et al.	1984	Basler et al.	1985	x		
66246-88-6	Penconazole	3	rat	feed	Basler et al.	1982	Basler et al.	1985	x		
66246-88-6	Penconazole	3	rat	feed	Basler et al.	1983	Basler et al.	1985	x		
66246-88-6	Penconazole	3	rat	feed	Hiles	1987	Basler et al.	1985	x		
67306-03-0	Fenpropimorph	3	rat	feed	Kirsch et al.	1979	Hunter et al.	1982		x	p
67306-03-0	Fenpropimorph	2	rat	feed	Kirsch et al.	1979	Hunter et al.	1982	x		
67306-03-0	Fenpropimorph	2	rat	feed	Kirsch et al.	1979	Hunter et al.	1982		x	p
68359-37-5	cyfluthrin	1	rat	inhalation	Thyssen and Mohr	1980	Pauluhn and Mohr	1984	x		
68359-37-5	cyfluthrin	1	rat	inhalation	Thyssen and Mohr	1980	Pauluhn and Mohr	1984	x		
68359-37-5	cyfluthrin	3	rat	feed	Loser and Schilde	1980	Suberg and Loser	1983	x		
68359-37-5	cyfluthrin	3	rat	feed	Oikawa et al.	1983	Suberg and Loser	1983		x	p
68439-50-9	C12-14AE7	1	rat	feed	Unilever	1977	Unilever	1978	x	x	s
68515-48-0	Di-isononyl phthalate (DINP1)	3	rat	feed	bio/dynamics	1982	Lington AW et al. Exxon Biomediacl Science	1997 1986	x		
68515-48-0	Di-isononyl phthalate (DINP1)	3	rat	feed	bio/dynamics	1982	Lington AW et al. Exxon Biomediacl Science	1997 1986		x	
68890-70-0	C12-15AS Na	2	rat	feed	HERA	2002	HERA	2002	x	x	s
68890-70-0	C12-15AS Na	1	rat	feed	HERA	2002	HERA	2002	x	x	s
68890-70-0	C12-15AS Na	3	rat	feed	HERA	2002	HERA	2002	x	x	s
84852-15-3	4-Nonylphenol branched	1	rat	feed	Hüls AG, Hazleton UK	1989	Chem Manufact. Assoc. Corning Hazelton Hard GC Cunny et al.	1997 1998 1997	x		
85117-50-6	LAS	3	rat	feed	Oser et al.	1965	Buehler EV et al.	1971	x		
85117-50-6	LAS	3	rat	feed	Kay JH et al.	1965	Buehler EV et al.	1971	x		
85509-19-9	flusilazole	3	rat	feed	Keller	1992	Pastoor et al.	1986	x		
85509-19-9	flusilazole	3	rat	feed	Keller	1992	Pastoor et al.	1986		x	p
86014-79-1	C13-C15 AS Na	1	rat	feed	HERA	1976	HERA	2002	x	x	s
95912-86-0	C8-10, C12-18-alkyl esters	1	rat	gavage	confidential		confidential		x	x	s

99129-21-2	2-(1-(((3-chloro-2-propenyl)oxy)imino)propyl)-5-(2-(ethylthio)propyl)-3-hydroxy- 2-cyclohexen-1-one	3	rat	feed	Dougherty et al.	1987	Dougherty et al.	1988	x	x	p
106232-83-1	C12-15AE7	1	rat	feed	Unilever	1977	Unilever	1978	x	x	s
120944-68-5	C14-15AE7	3	rat	feed	Shell Research Ltd.	1982	Talmage S	1994	x		
120944-68-5	C14-15AE7	3	rat	feed	Shell Research Ltd.	1982	Talmage S	1994		x	s
125301-92-0	NaC12-15E3S	1	rat	feed	Unilever	1980	Shell Research Ltd	1982	x		
125301-92-0	NaC12-15E3S	1	rat	feed	Unilever	1980	Shell Research Ltd	1982		x	s
134098-61-6	Fenpyroximate	3	rat	feed	Aughton	1987	Aughton	1989	x	x	p
S1	S1	1	rat	gavage	confidential		confidential		x		
S2	S2	1	rat	gavage	confidential		confidential		x	x	s