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Final

APPLICATION FOR AUTHORISATION: ESTABLISHING A REFERENCE DOSE RESPONSE RELATIONSHIP FOR CARCINOGENICITY OF TRICHLOROETHYLENE

Background

At the 22nd meeting of the Committee for Risk Assessment (RAC) in September 2012, the ECHA Secretariat presented a proposal to set DNELs and dose response relationships for substances prior to receiving applications for authorisation (AfAs). This was approved by RAC as a trial exercise.

The DNELs and dose response relationships so derived will serve as a non-legally binding 'reference value'. They would provide applicants with a clear signal as to how RAC is likely to evaluate these important elements of the risk assessment of AfA.

This initiative is intended to improve the efficiency of the AfA process as a whole by discussing and when possible publishing reference values or dose response relationships in advance of applications, so providing greater consistency and better use of the legally defined periods of opinion-development in the RAC. The trial will be evaluated in terms of efficiency after the first applications have been discussed in the Committee.

Requested action:

Following the Committee's agreement on the document, it will be published on the ECHA website.

Annex 1: Reference dose response relationship for carcinogenicity of trichloroethylene

Annex 1 Reference dose response relationship for carcinogenicity of trichloroethylene

Trichloroethylene (CAS 79-01-6) is included in Annex XIV of REACH "List of substances subject to authorisation".

Relevance of endpoints

For applicants applying for authorisation under Article 60(2) (adequate control route), in order to conclude whether the adequate control is demonstrated, only endpoints (i.e. properties of concern) for which the substance is included in Annex XIV need to be addressed in the hazard assessment[1]. However, information on other endpoints might be necessary for comparing the risks with the alternatives.

For applicants aiming at authorisation based on Article 60(4) (socio-economic analysis route) Article 62(4)(d) also applies and the socio-economic analysis (SEA) route will as a consequence focus on the risks that are related to the intrinsic properties specified in Annex XIV. The SEA should in turn consider the impacts related to such risks. In practice the applicant is expected to provide this information in their (Chemical Safety Report) CSR for which an update may be advisable. However, for an authorisation to be granted, the applicant should also demonstrate that there are no suitable alternatives. In this latter analysis it may be the case that other endpoints than those for which the substance was listed in 'Annex XIV' become relevant in order to demonstrate that no suitable alternative is available.

Trichloroethylene was included on Annex XIV due to its carcinogenic properties. The reference dose response relationships proposed in the present document are only based on carcinogenicity arising from trichloroethylene exposure[2].

Carcinogenicity

Larsen & Giovalle (2014) provided a review of the carcinogenic dose-response relationship of trichloroethylene. This review was focused on a series of Expert assessments conducted since the year 2000. Table 1 below gives an overview of these assessments, the assumed carcinogenic mechanism, and the low-dose extrapolation approaches that were used:

[1] Article 60(2) states "…an authorisation shall be granted if the risk to human health or the environment from the use of the substance arising from **intrinsic properties specified in Annex XIV** is adequately controlled."

[2] Endpoints relevant to the authorisation are also discussed in section 5 of the document: "How RAC and SEAC intend to evaluate the applications" (common approach of RAC and SEAC in opinion development on applications for authorisation, agreed RAC-20/SEAC14, 24/03/2012). Link: http://echa.europa.eu/web/guest/applying-for-authorisation/additional-information

Table 1 Overview of the findings of Expert assessments on the carcinogenic mode of action of trichloroethylene (Larsen & Giovalle 2014)

Expert evaluation	Primary mechanistic concern	Threshold / Non-threshold approach	Studies / effects of most concern for Point Of Departure	Unit risk/ Slope factor / Threshold dose
WHO (2000)	Genotox	Non-threshold linear approach	Maltoni et al (1986) - Rats - Inhalation - Leydig tumors	Unit risk, 24 hr exp. 4.3×10^{-4} $(mg/m^3)^{-1}$
EU-RAR (2004)	Genotox + cytotox	Non-threshold	Focus on exp. animal studies - kidney cancer POD not defined	Not addressed
WHO (2005)	Genotox	Non-threshold linear approach	NTP (1990) - Rats - Oral - Kidney cancer	Unit risk, 24 hr exp. 7.8×10^{-4} $(mg/kg\ bw\ d)^{-1}$
AGS (2008)	Genotox + Cytotox	Non-threshold Sublinear approach	Henschler et al. (1995) Vamvakas et al. (1998) Brüning et al. (2003) Green et al. (2004) Seldén et al. (1993) - Humans - Inhalation - Kidney cancer + cytotox	Slope factors, 8 hr exp. Above 6 ppm: 1.31×10^{-4} $(mg/m^3)^{-1}$ Below 6 ppm: 1.22×10^{-5} $(mg/m^3)^{-1}$
SCOEL (2009)	Cytotox + Genotox	Practical threshold*	Brüning et al. (2003) Raashcou-Nielsen et al. (2003) Charbotel et al. (2006) Green et al. (2004) Seldén et al. (1993) - Humans - Inhalation - Kidney cancer + cytotox	Threshold, 8 hr exp: 57 mg/m^3 (as NOAEL and OEL)

Expert evaluation	Primary mechanistic concern	Threshold / Non-threshold approach	Studies / effects of most concern for Point Of Departure	Unit risk/ Slope factor / Threshold dose
WHO (2010)	Genotox	Non-threshold linear approach	Maltoni et al (1986) - Rats - Inhalation - Leydig tumors	Unit risk, 24 hr exp. 4.3 × 10-4 $(mg/m^3)^{-1}$
US-EPA (2011)	Genotox	Non-threshold linear approach	Charbotel et al. (2006) - Humans - Inhalation - Kidney cancer	Unit risk, 24 hr exp. Inhalation: 1×10^{-3} $(mg/m^3)^{-1}$ Oral: $1{,}0 \times 10^{-2}$ (mg/ kg bw d)$^{-1}$
IARC (2012 evaluation)**	Genotox	Not stated	Overall epidemiological evidence with focus on kidney cancer No POD identified	Not addressed
HSE (2012)	Not addressed	Cancer incidences only estimated considered existing high occupational exposures	Review paper by Wartenberg et al. (2000) - Humans - Inhalation - Kidney cancer	Not addressed
Afsset (2009) **/** **Anses (2013)**	Genotox	Non threshold linear approach	As WHO (2000) Maltoni et al (1986). - Rats - Inhalation - Leydig tumors	Unit risk, 24 hr exp. 4.3×10^{-4} $(mg/m^3)^{-1}$

* The strategy of SCOEL for deriving OELs for carcinogens and mutagens has been described by Bolt & Huici-Montagud (2008). Here carcinogenic substances are differentiated into four classes in relation to methods for the OEL derivation:

*(C) Genotoxic carcinogens with a **practical** threshold, as supported by studies on mechanisms and/or toxicokinetics; health-based exposure limits may be based on an established NOAEL (no observed adverse effect level).*

*(D) Non-genotoxic carcinogens and non-DNA-reactive carcinogens; for these compounds a **true ("perfect")** threshold is associated with a clearly founded NOAEL. The mechanisms shown by tumour promoters, spindle poisons, topoisomerase II poisons and hormones are typical examples of this category.*

** Rusyn et al. (2013), publication giving an extended summary of the IARC 2012 evaluation.

Trichloroethylene is classified in the EU as Muta 2; H341 according to the CLP Regulation, (EC) 1272/2008. Studies on trichloroethylene itself show that trichloroethylene did not induce gene mutations in most standard mutation bacterial assays (studies performed without mutagenic stabilizers and without metabolic activation) whereas it was found positive in some fungal and yeast systems. In mammalian systems, trichloroethylene showed the ability to induce DNA and chromosome damages in some in vitro and in vivo studies, but not in others. Rather than a

direct acting genotoxic substance, there is evidence supporting the fact that trichloroethylene can bind to nucleic acids and proteins after bio-activation. This DNA binding ability would be consistent with an ability to induce DNA and chromosomal perturbations. The metabolic pathway of trichloroethylene plays a key role for understanding the mechanistic actions regarding the carcinogenicity of trichloroethylene including its genotoxic mechanism. The major metabolic pathway - the oxidative CYP-mediated pathway - leads to the formation of oxidation products such as chloral (C), chloral hydrate(CH), trichloroacetic acid (TCA), trichloroethanol (TCOH), trichloroethanol glucuronide, dichloroacetyl chloride (DCAC), dichloroacetic acid (DCA), oxalic acid and increased levels of formic acid. Of these metabolites, CH was found positive in bacterial mutation tests for point mutations and in the mouse lymphoma assay. Further, DCA was found to be mutagenic *in vitro* in the *S. typhimurium* assays, in the mouse lymphoma assay, and also in *in vivo* cytogenetic tests, in the micronucleus test, and in the Big Blue mouse system.

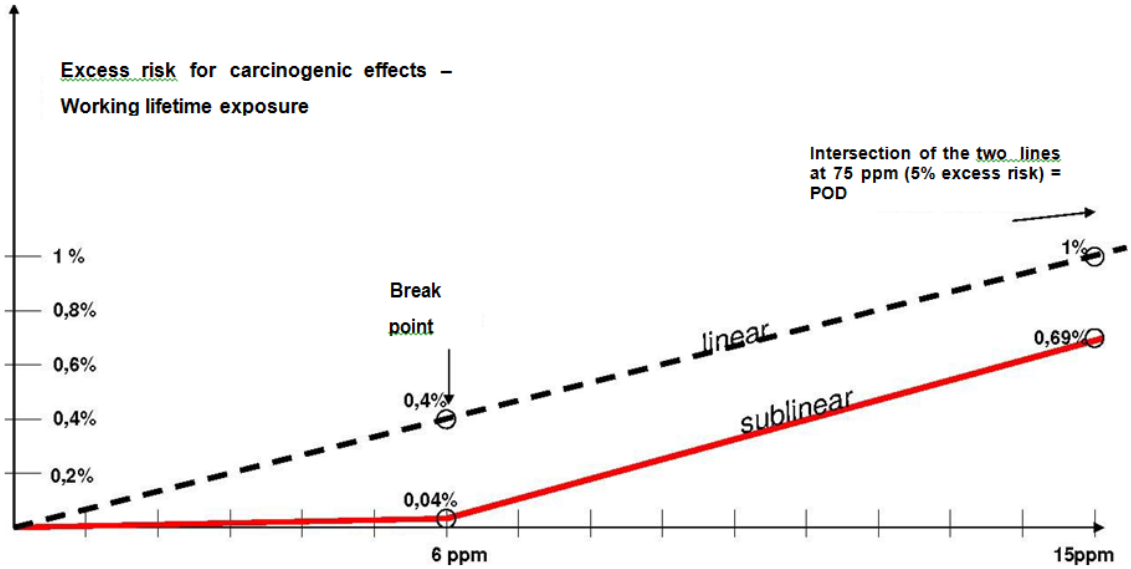
The minor metabolic pathway – the reductive glutathione mediated pathway, GSH - is a metabolic pathway that especially operates when the oxidative pathway becomes saturated. This metabolic pathway leads to the formation of dichlorovinylglutathione (DCVG) which is further converted to dichlorovinylcysteine (DCVC). DCVC is then further converted to several reactive metabolites by beta-lyase conversion or deactivated by N-acetylation leading to NAcDCVC. The metabolites DCVG, DCVC and the further activated metabolites of DCVC are considered as direct acting genotoxic substances, and DCVC has been found as a strong direct acting mutagen in bacteria both with and without metabolic activation; additionally, primary DNA damage in mammalian cells *in vitro* and *in vivo* has been observed. After *in vivo* exposure to trichloroethylene, the metabolites DCVG, DCVC, and NAcDCVC have all been detected in the blood, kidney, or urine of rats, and DCVG has been detected in human blood and NAcDCVC in urine. Thus, this metabolic pathway is believed to be crucial for the understanding of the formation of kidney cancer, as these genotoxic metabolites are either being delivered to or produced in the kidney (US EPA 2011). Also, human data has indicated that kidney cancer risk was attenuated in trichloroethylene exposed individuals lacking this GSH conjungation gene (leading to the blockage of formation of DCVG and DCVC metabolites; Rusyn et al. 2013).

Based on these findings it is concluded that due to the genotoxic potential trichloroethylene should be evaluated as a non-threshold carcinogen with respect to risk characterisation. This view is supported by the majority of the expert evaluations as indicated in table 1 above. Especially the findings of kidney cancer in epidemiological studies and the formation of the genotoxic substances DCVG and DCVC *in situ* in the kidneys of humans have placed the focus on the epidemiological studies when characterising the risk of trichloroethylene. Thus, human data on the formation of renal cell carcinoma in the occupational environment is considered to be especially relevant for establishing a dose-response relationship for this substance.

In the epidemiological studies, increased risk of kidney cancer was found at relatively high occupational exposure including very high peak exposures altogether leading to cytotoxic responses noted as renal tubular damage in the kidneys. The cytotoxic effects are considered to enhance the carcinogenic response and thus the risk for kidney cancer is considered to be much lower below cytotoxic levels. Therefore a linear dose-response relationship would overestimate the risk at low exposure levels. Taking account of this, the sublinear approach concluded by AGS (2008), is considered to be the most scientifically justified as uniquely of those reviews listed in table 1, it includes these aspects.

The starting point used by AGS (2008) was three German epidemiological studies by Henschler et al. (1995), Vamvakas et al. (1998), and Brüning et al. (2003) from which an excess risk of 5% was estimated based on a cumulative exposure of 3000 ppm-years, corresponding to a 40 years average occupational exposure of 75 ppm. From this data-point, a linear non-threshold dose-response curve was established (the dotted line in figure 1). AGS (2008) considered 6 ppm as a threshold for cytotoxic (and co-carcinogenic) effects in the kidneys and down-scaled the risk at 6ppm and below with a factor of ten in order to consider the lowered risk below the cytotoxic levels. Using this approach, a sublinear non-threshold approach was obtained which took into account both the genotoxic mechanism as well as the cytotoxic co-carcinogenic mechanism that operates at the higher dose levels. Thus, the dose-response curve becomes steeper above the threshold level of 6 ppm for the cytotoxic effects, see red line in figure 1 below:

Figure 1. Excess risk for carcinogenic effects-Working lifetime exposure



The dose-response relationship was mathematically expressed (AGS (2008)):

At 6 ppm and above:

Excess risk (kidney cancer) = 7.2×10^{-4} ppm^{-1} × concentration (ppm) – 0.0039

Below 6 ppm:

Excess risk (kidney cancer) = 6.7×10^{-5} ppm^{-1} × concentration (ppm)

RAC discussed whether the level for cytotoxic effects in the kidneys should be set at 6 ppm as concluded by AGS (2008) or at 10 ppm as concluded by SCOEL (2007). Both expert groups referred to a study by Selden et al. (1993) that found no increased level of the biomarker N-acetyl-ß-D-glucosaminidase (NAG) in urine among 29 workers exposed to relatively low levels of trichloroethylene (NAG in urine was used as an indicator for subclinical kidney damage). Both AGS (2008) and SCOEL (2007) made their conclusion on the no effect level for cytotoxicity with reference to the majority of the data-points/ workers in the study. Thus, AGS (2008) referred to 23 of the lowest exposed workers and SCOEL (2007) referred to 25 of the lowest exposed workers among the total of 29 workers. The Selden et al. (1993) study included a table showing the average exposure level measured by air sampling for a one week working period of the workers. The table actually showed that *25* of the workers were exposed at or below exposures up to 30-39 mg/m^3 (average of this range is 34.5 mg/m^3 or approximately equivalent to 6 ppm). No workers were exposed at the next exposure range from 40 and up to 49 mg/m^3 (9 ppm). Furthermore, three workers were exposed at levels in

the range of 50-99 mg/m^3 and one worker above 100 mg/m^3 but these four data points were not specifically addressed by AGS (2008) and SCOEL (2007) as they made their conclusion based on the majority of the data-points below these levels.

In conclusion no sign of subclinical kidney toxicity was noted in this study. When deciding on a no effect level for subclinical effects in the kidneys a level of 6 ppm is the most relevant and justified figure to use as this reflects the upper average exposure level for 25 of the 29 workers.

Bioavailability

The dose-response relationship for trichloroethylene was derived from occupational exposure and measurements and estimations of inhalation exposure levels. As no specific human data is available concerning dose-response from oral and dermal exposure, route-to-route extrapolations had to be performed in order to obtain dose-response relationships for oral and dermal exposure. Due to a lack of valid data on a dermal absorption rate the route-to-route extrapolation from inhalation exposure to dermal was performed, anticipating the same absorption rate for both exposure routes. For inhalation to oral exposure, human data indicating an absorption rate by inhalation of 40% was used and an oral absorption rate of 90% was used based on animal data (90% absorption for fasted rats) (according to data from US-EPA 2011).

Carcinogenicity risk assessment

The following dose-response for excess risk for occupational exposure to trichloroethylene was established by AGS (2008):

At 6 ppm and above:
Excess risk = 7.2×10^{-4} ppm^{-1} × concentration (ppm) – 0.0039

Below 6 ppm:
Excess risk = 6.7×10^{-5} ppm^{-1} × concentration (ppm)

Expressed in mg/m^3 (1 ppm = 5.47 mg/m^3) this corresponds to

At 33 mg/m^3 and above:
Excess risk = 1.3×10^{-4} (mg/m^3)$^{-1}$ × concentration (mg/m^3) – 0.0039

Below 33 mg/m^3:
Excess risk = 1.2×10^{-5} (mg/m^3)$^{-1}$ × concentration (mg/m^3)

From these equations further dose-response relationships were then calculated for:
- continuous inhalational exposure for the general population
- dermal exposure for workers
- dermal exposure for the general population
- oral exposure for the general population

Inhalation exposure

Workers

Based on 8h exposure 5 days/week during 40 years, the risk estimates are:

At 33 mg/m^3 and above:
Excess risk = 1.3 × 10^{-4} (mg/m^3)$^{-1}$ × concentration (mg/m^3) – 0.0039

Below 33 mg/m^3:
Excess risk = 1.2 × 10^{-5} (mg/m^3)$^{-1}$ × concentration (mg/m^3)

Table 2 Excess lifetime kidney cancer risk estimated for workers exposed at different 8h-TWA concentrations of trichloroethylene for 40 years

TWA trichloroethylene concentration (mg/m^3)	Excess kidney cancer risk in EU workers (×10^{-4})
400	481
300	351
100	91.0
60	39.0
40	13.0
33 (6ppm)*	**4.0**
20	2.4
10	1.2
5	0.6
1	0.12
0.1	0.012

* break-point for the sublinear dose-response curve

General population

For transforming the equations above from occupational exposure to continuous population exposure over 70 years an adjustment factor of 5.3 was used in relation to the slopes of the curves and the break point of the curve:

Adjustment factor= 20m^3/d / 10m^3/d × 7d/5d × 52w/48w × 70y/40y = *5.3*

Using this adjustment factor for the break point level and the dose-response slopes this results in the following dose-response equations:

At 6.2 mg/m^3 and above:
Excess risk = 6.9 × 10^{-4} (mg/m^3)$^{-1}$ × concentration (mg/m^3) – 0.0039

Below 6.2 mg/m^3:
Excess risk = 6.4 × 10^{-5} (mg/m^3)$^{-1}$ × concentration (mg/m^3)

Table 3 Excess lifetime kidney cancer risk estimated for the general population exposed at different 24-h average concentrations of trichloroethylene for 70 years

Trichloroethylene 24-h concentration (mg/m^3)	Excess kidney cancer risk in EU general population ($\times 10^{-4}$)
60	375.0
30	168.0
20	99.0
10	30.0
6.2*	**4.0**
3	1.9
1	0.6
0.1	0.06
0.01	0.006

* break-point for the sublinear dose-response curve

Dermal exposure

Workers

Due to lack of valid data for a dermal absorption rate, the route-to-route extrapolation from inhalation to dermal exposure was performed, anticipating the same absorption rate for both exposure routes.

With this approach, *1 mg/m^3* occupational exposure during a day corresponds to a dermal dose of *0.143 mg/kg bw/d* (for an adult worker of 70 kg inhaling 10m^3 of air). Using this proportionality, the equations for inhalation exposure can be transformed to a dose-response relationship for dermal exposure in workers:

At 4.72 mg/kg bw/d and above:
Excess risk = 9.09×10^{-4} $(mg/kg\ bw/d)^{-1}$ × dose (mg/kg bw/d) – 0.0039

Below 4.72 mg/kg bw/d:
Excess risk = 8.4×10^{-5} $(mg/kg\ bw/d)^{-1}$ × dose (mg/kg bw/d)

Table 4 Excess lifetime kidney cancer risk estimated for workers exposed at different dermal dose levels of trichloroethylene for 40 years

Trichloroethylene dermal dose (mg/kg bw/d)	Excess kidney cancer risk in EU workers ($\times 10^{-4}$)
50	416
30	234
10	52
4.72*	**4.0**
1	0.84
0.5	0.42
0.1	0.084
0.01	0.0084
0.001	0.00084

* break-point for the sublinear dose-response curve

General population

The dose-response for dermal exposure of workers can be transformed to dose-response for dermal exposure in the general population by applying an adjustment factor of 2.3 taking account of differences in exposure duration and average body weight in the default assumptions for workers and the general population:

Adjustment factor = 7d/5d × 52w/48 w × 70y/40y × 60kg/70kg = *2.3*

Using this adjustment factor for the break point level and the dose-response slopes for dermal exposure to workers this result in the following dose-response equations for dermal exposure to the general population:

At 2.05 mg/kg bw/d and above:
Excess risk = 2.09 × 10^{-3} (mg/kg bw/d)$^{-1}$ × dose (mg/kg bw/d) – 0.0039

Below 2.05 mg/kg bw/d:
Excess risk = 1.9 × 10^{-4} (mg/kg bw/d)$^{-1}$ × dose (mg/kg bw/d)

Table 5 Excess lifetime kidney cancer risk estimated for general population exposed at different daily dermal dose levels of trichloroethylene for 70 years

Trichloroethylene dermal dose (mg/kg bw/d)	Excess kidney cancer risk in EU general population (×10^{-4})
30	588
10	170
5	65.5
3	23.7
2.05*	**4.0**
1	1.9
0.1	0.19
0.01	0.019
0.001	0.0019

* break-point for the sublinear dose-response curve

Oral exposure

Workers

By convention usually not relevant for workers.

General population

Route-to-route extrapolation has to be applied in order to transform the inhalation dose-response relationship for the general population to an oral dose-response. For this data, an inhalation absorption rate of 40% and an oral absorption rate of 90% were used based on data presented by US-EPA (2011). When an adult person weighing 60 kg inhales 20m^3 air per day at a concentration of *1 mg/m^3* this then with the above mentioned absorption rates corresponds to an oral dose of *0.148 mg/kg bw/d*.

Using this relationship the inhalational dose-response can be converted to an oral dose-response relationship of:

At 0.92 mg/kg bw/d and above:
Excess risk = 4.66×10^{-3} (mg/kg bw/d)$^{-1}$ × dose (mg/kg bw/d) – 0.0039

Below 0.92 mg/kg bw/d:
Excess risk = 4.32×10^{-4} (mg/kg bw/d)$^{-1}$ × dose (mg/kg bw/d)

Table 6 Excess lifetime kidney cancer risk estimated for the general population exposed at different oral daily doses of trichloroethylene for 70 years

Trichloroethylene oral dose (mg/kg bw/d)	Excess kidney cancer risk in EU general population ($\times 10^{-4}$)
30	1359
10	427
1	7.6
0.92*	**4.0**
0.5	2.16
0.1	0.43
0.01	0.043
0.001	0.0043

* break-point for the sublinear dose-response curve

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