ANSES Opinion
Request No 2019-SA-0073

The Director General

Maisons-Alfort, 12 January 2021

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the development of a chronic TRV by the respiratory route for 1,3-butadiene (CAS No. 106-99-0)

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It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 12 January 2021 shall prevail.

On 11 April 2019, ANSES received a formal request from the Directorate General for Health (DGS) and the Directorate General for Risk Prevention (DGPR) to carry out the following expert appraisal: formal request on the selection or development of toxicity reference values (TRVs) for 1,3-butadiene.

1. BACKGROUND AND PURPOSE OF THE REQUEST

A toxicity reference value, or TRV, is a toxicological indicator for qualifying or quantifying a risk to human health. It establishes the link between exposure to a toxic substance and occurrence of an adverse health effect. TRVs are specific to a duration (acute, subchronic or chronic) and route (oral or respiratory) of exposure. The way TRVs are established differs depending on the knowledge or assumptions made about the substances' mechanisms of action. Currently, the default assumption is to consider that the relationship between exposure (dose) and effect (response) is monotonic. In the current state of knowledge and by default, it is generally considered that for non-carcinogenic effects, toxicity is only expressed above a threshold dose (ANSES, 2017).

In practice, establishing a TRV involves the following steps:

- identifying and analysing the available toxicity data, based on epidemiological and/or experimental studies;
- identifying the target organ(s) and critical effect;
- identifying the assumption according to which it is established: with or without a threshold dose, depending on the substance's mode of action;
- choosing a good-quality scientific study generally enabling a dose-response relationship to be established;

- defining a critical dose for humans or animals from this study and, if required, in the case of a critical dose obtained in animals, adjusting this dose to humans;
- for a threshold TRV, applying uncertainty factors to this critical dose so as to derive a TRV that is applicable to the entire population;
- for a non-threshold TRV, conducting a linear extrapolation to the origin in order to determine an excess risk per unit.

TRVs are formulated according to a highly structured and rigorous approach involving collective assessments by groups of specialists.

Following the publication in June 2018 of ANSES's collective expert appraisal report on “Emerging pollutants in ambient air” which recommends the national monitoring of 1,3-butadiene, together with a proposed environmental objective related to the protection of human health, several Regional Directorates for the Environment, Land Planning and Housing (DREAL) proposed prefectural orders with a view to either revising the health risk assessments (HRAs) of manufacturers or developing an environmental monitoring system for this pollutant (ANSES, 2018).

For carcinogenic effects, several organisations have established unit risk (UR) values. In the HRAs conducted before 2011, the UR of the United States Environmental Protection Agency (US EPA) (2002) was most frequently used. However, in 2011, the National Institute for Industrial Environment and Risks (INERIS) used the Office of Environmental Health Hazard Assessment (OEHHA) (2011, revised in 2013) UR in its HRAs of classified installations for the protection of the environment (ICPE) in accordance with information note No. DGS/EA1/DGPR/2014/307 of 31 October 2014 on the methods for selecting chemical substances and choosing TRVs in order to conduct HRAs in the framework of impact and management studies for polluted sites and soils. Since then, new studies have been published and a new carcinogenic TRV has been established by the Texas Commission on Environmental Quality (TCEQ) (2008 but published with free access in 2013). In its most recent expert appraisal dating from 2019, INERIS modified the choice made in 2011 and ultimately selected the TRV of the US EPA, based on human data. Depending on the UR used, risks can become unacceptable in the HRAs conducted in certain industrial areas of France.

On 11 April 2019, in light of the various TRVs currently available for 1,3-butadiene that may or may not entail an acceptable risk depending on which one is used, ANSES received a formal request from the DGS and DGPR to select or develop chronic TRVs by inhalation (with and without a threshold).

The nature of the TRVs (acute, subchronic and chronic) is partly determined by the duration of exposure in the toxicological studies but also by the health risk assessment needs. As a reminder, when assessing health risks in humans, ANSES distinguishes between three types of exposure duration:

- Acute exposure, from a few hours to a few days;
- Subchronic exposure, from a few days to a few months;
- Chronic exposure, from one or more years to an entire lifetime.

Chronic TRVs are used to protect the entire population, including susceptible population groups such as children, from the effects of a substance following chronic exposure, i.e. for more than one year.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 “Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)”.

The collective expert assessment was carried out by the Expert Committee (CES) on “Health reference values”. The methodological and scientific aspects of the work were regularly presented to the CES between October 2019 and November 2020. The work was adopted by the CES on 10 December 2020.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals. The experts’ declarations of interests are published on the ANSES website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE CES

■ Summary of the toxicological data

The summary of the toxicological data was based on summary reports by internationally recognised organisations (US EPA, 2002; JRC, 2002; AFSSET, 2010; INERIS, 2019; ANSES, 2019), supplemented by a literature search conducted for the 2008-2019 period. In connection with the background of the request, the analysis focused on the observed toxic effects of chronic exposure by inhalation.

- Toxicokinetics

1,3-butadiene enters the body mainly via the respiratory tract (ANSES, 2019). In rodents, the substance and its metabolites are primarily concentrated in the blood, respiratory tract, intestines, liver, kidneys, bladder and pancreas (ANSES, 2019).

1,3-butadiene is mainly oxidised to 1,2-epoxy-3-butene (EB) under the action of cytochrome P450 enzymes (CYP2E1 and CYP2A6) and then to 1,2,3,4-diepoxybutane (DEB) via CYP2E1 and also CYP2A and CYP2C9 to a lesser extent; it may also be hydrolysed to 1,2-dihydroxy-3-butene (or butenediol) by epoxide hydrolase (EH). However, there are quantitative differences in the kinetics of 1,3-butadiene depending on the species. For example, the oxidation rate (V_{max}/K_m)[1] is higher in mice than in humans and rats, which have similar levels. 1,3-butadiene epoxides are primarily eliminated after conjugation in rodents, unlike in humans where they are mainly eliminated after hydrolysis (ANSES, 2019). The metabolism of 1,3-butadiene can be modulated by certain polymorphisms in genes encoding for enzymes such as CYP2E1 and for glutathione S-transferases M1 (GSTM1) and T1 (GSTT1). Certain activity phenotypes in these enzymatic systems can promote the formation of genotoxic epoxides and/or limit their elimination.

1,3-butadiene is excreted via exhaled air in the form of CO_2 and in urine and faeces in the form of two major metabolites: monohydroxybutenylmercapturic acid (MHBMA) and dihydroxybutylmercapturic acid (DHBMA) (ANSES, 2019).

[1] Maximum velocity/Michaelis constant

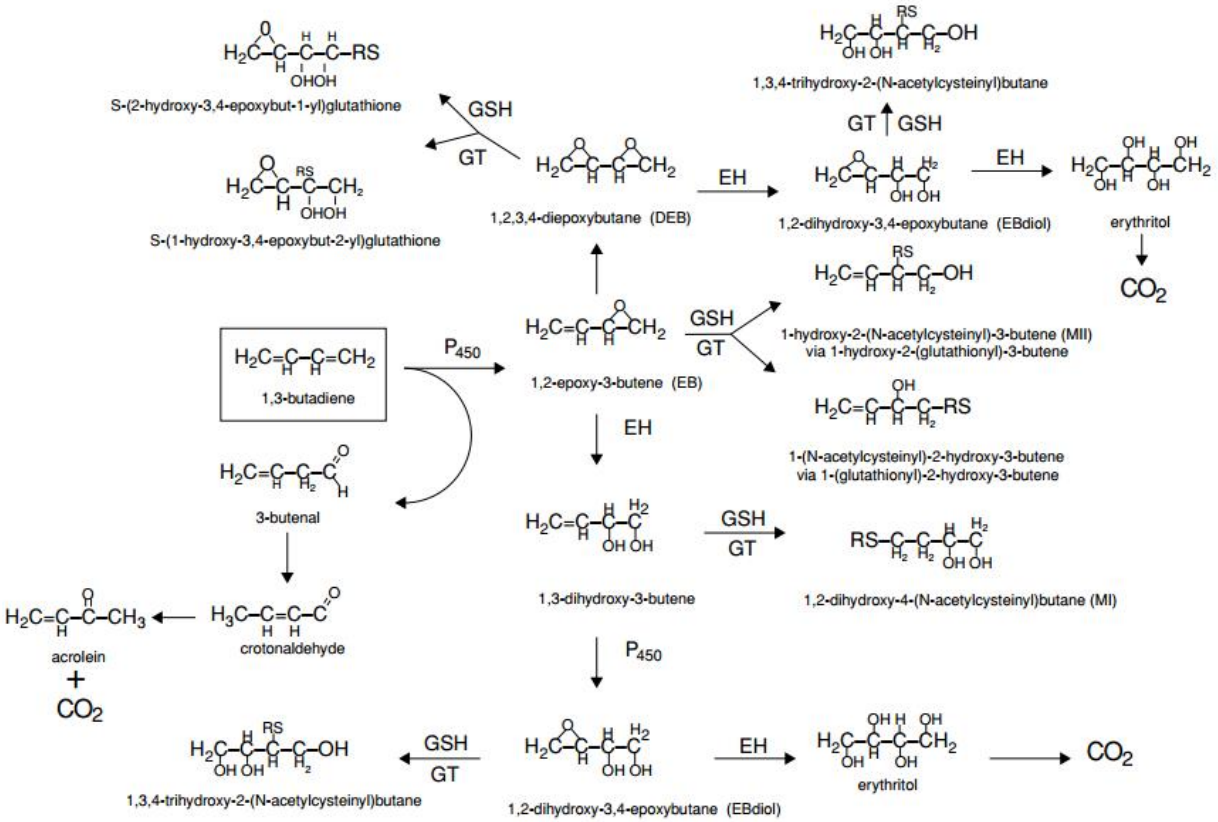

Figure 1: Diagram representing the metabolism of 1,3-butadiene

- Acute effects

LC_{50}[2] values of over 100,000 ppm have been noted in mice after inhalation for exposure durations of up to four hours. In humans, the main clinical sign is eye, nose and mouth irritation occurring at high concentrations during occupational exposure. Non-specific neurological symptoms (fatigue and drowsiness) have also been reported (JRC, 2002; AFSSET, 2010; INERIS, 2019).

- Subchronic and chronic effects

Some epidemiological data have shown, among other things, increased mortality from cardiovascular diseases (arteriosclerotic heart disease, cardiac ischaemia, etc.), some minor haematological effects (reduced numbers of red blood cells, platelets, neutrophils and haemoglobin, etc.), and neurotoxic effects. All of these studies had methodological limitations relating to the exposure data and the presence of confounding factors.

In animals, the toxicity of 1,3-butadiene after repeated exposure by inhalation has mainly been studied in mice and rats. The main induced effects included atrophy of the reproductive organs, hepatic necrosis, anaemia, various lesions in the nasal cavity, hyperplasia of the cardiac endothelial cells, alveolar epithelial cells and forestomach (mice), and renal lesions (male rats). The observed effects were more severe in mice than in rats and occurred at various concentrations. In a two-year

[2] Concentration that will lead to the death of 50% of tested animals

study in mice, the critical effect was ovarian atrophy, whose incidence significantly increased at all the tested concentrations. Examination of these results led the CES to propose a LOAEC[3] of 14 $mg \cdot m^{-3}$ for these effects.

- Effects on reproduction and development

No OECD guideline studies for analysing effects on reproduction are available for 1,3-butadiene. In repeated toxicity studies, an increase in the incidence of ovarian atrophy was observed in mice at all the tested concentrations (≥ 14 $mg \cdot m^{-3}$). An increase in testicular and uterine atrophy as well as hyperplasia of the germinal epithelial and granulosa cells have been reported at higher concentrations (primarily ≥ 450 $mg \cdot m^{-3}$) (NTP, 1993).

Various bone malformations have been observed in rat foetuses after *in utero* exposure to 1,3-butadiene at concentrations between 450 and 18,000 $mg \cdot m^{-3}$. These effects occurred in a context of maternal toxicity represented by a statistically significant decrease in body weight gain or even weight loss for all the exposure concentrations (Irvine, 1981). This type of effect was not found in another prenatal toxicity study in rats and mice (Hackett *et al.*, 1987; Morrissey *et al.*, 1990).

- Genotoxicity

In Europe, 1,3-butadiene is classified as a Category 1B germ cell mutagen (may cause genetic defects). 1,3-butadiene has proven to be mutagenic in *in vitro* and *in vivo* studies. It has clearly been shown that the genotoxic effects induced by 1,3-butadiene involve enzymatic activation to active electrophilic metabolites, primarily DEB, EB and possibly EBdiol (monoepoxide diol). Of these epoxides, DEB is considered as the most genotoxic metabolite via the induction of large deletions. EB mainly induces point mutations and small deletions (US EPA, 2002). Therefore, the genotoxicity of 1,3-butadiene can be modulated by certain polymorphisms in the genes encoding for CYP2E1, GSTM1 and GSTT1 (Fustinoni *et al.,* 2002).

- Carcinogenicity

In Europe, 1,3-butadiene is classified as a Category 1A carcinogen (may cause cancer). It has also been classified in Group 1 (carcinogenic to humans) by the IARC (IARC, 2008 & 2012). There is strong evidence that the carcinogenicity mechanism is related to genotoxicity mediated by epoxide metabolites.

The available epidemiological data come from occupational cohorts of workers in the synthetic rubber (styrene-butadiene) industry or producing butadiene monomer. These studies assessed the causal relationship between the occurrence of tumours and exposure to 1,3-butadiene.

The largest cohort of workers in the butadiene monomer production industry was initiated by Downs *et al.* (1987) in the United States and then regularly updated (Divine, 1990; Divine *et al.,* 1993; Divine and Hartman, 1996; Divine and Hartman, 2001). The various analyses showed an increase in deaths from lymphatic and haematopoietic tissue cancer (lymphosarcoma and non-Hodgkin's lymphoma) (SMR = 141; $CI_{95\%}$: 105-186). This increase was found in the sub-groups of workers recruited before 1950 and workers who had been employed for less than five years (Divine and Hartman, 2001).

The largest study conducted in the synthetic rubber production industry was initiated by Delzell *et al.* in 1996 and then regularly updated (data last updated in 2009 published in Sathiakumar *et al.,* 2019). This retrospective cohort study initially included 15,649 men spread out across eight North American facilities. As the study was updated, mortality was monitored over a longer period. Exposure estimates relied on job x exposure matrices using company archives, tasks and processes in use

[3] Lowest Observed Adverse Effect Concentration

over time and during atmospheric measurements taking distances and protective equipment into account. The various results consistently showed an association between exposure to 1,3-butadiene and deaths from all types of leukaemia. Sub-types of leukaemia were generally not specifically analysed, thus creating a group of non-comparable diseases. The two most recent studies of Sathiakumar *et al.* (2015 & 2019) presented the most complete analyses. In the latest publication, a statistically significant increase in cases was observed for all types of leukaemia, including lymphoid and myeloid leukaemia (SMR = 139; $CI_{95\%}$ = 106-179) and non-Hodgkin's lymphoma (SMR = 136; $CI_{95\%}$ = 102-177), for the sub-group of hourly employees who worked for at least 10 years. The internal Cox regression analysis of the continuous exposure variable showed a statistically significant positive dose-response relationship with 1,3-butadiene for all types of leukaemia combined ($p = 0.014$) and for lymphoid leukaemia ($p = 0.007$) but not for myeloid leukaemia ($p = 0.602$). Neither non-Hodgkin's lymphoma nor multiple myeloma appeared associated with exposure to 1,3-butadiene, whether in the external or internal analyses. The main limitations of this cohort study were its failure to take into account certain confounding factors such as smoking and its use of mortality instead of incidence (in particular considering that some cancers, such as leukaemia, can be associated with a long survival time).

Two-year studies in animals have reported neoplasms in multiple organs. Lymphomas in mice and mammary gland tumours in rats were the main cause of mortality. The other reported tumours in mice were cardiac hemangiosarcomas, pulmonary neoplasias, tumours of the forestomach (squamous cell papillomas and carcinomas), mammary gland (carcinomas, adenoacanthomas and malignant mixed tumours), ovaries (benign and malignant granulosa cell tumours) and liver (adenomas and carcinomas), and tumours of the harderian gland and preputial gland, renal tubule adenomas, brain neoplasms, intestinal carcinomas, skin sarcomas and Zymbal's gland tumours (NTP, 1993). In rats, tumours have been found in the mammary gland, thyroid, uterus and Zymbal's gland in females and in the exocrine pancreas and Leydig cells in males (Owen *et al.,* 1987; Owen and Glaister, 1990).

- **Chronic TRV by the respiratory route**
  - Choice of the critical effect

The CES decided to choose ovarian atrophy as the critical effect, as it occurs from the lowest concentration in mice after chronic exposure by inhalation. One of the assumptions put forward by the US EPA is the induction of ovarian atrophy following a decrease in the number of follicles ultimately promoting tumour formation. This effect is likely related to the formation of the DEB metabolite.

Uterine and testicular atrophy have also been observed in NTP[4] studies at higher concentrations. The US EPA (2002) suggested that uterine atrophy may be due to a decrease in oestrogen caused by ovarian atrophy. It seems that the testicles are less susceptible to the toxic effects of 1,3-butadiene than the ovaries.

[4] National Toxicology Program

- Analysis of the existing TRVs

Three TRVs are available: one developed by the US EPA in 2002, one by the TCEQ in 2008 and one by OEHHA in 2013 (see Table 1).

Table 1: List of the chronic threshold TRVs available for 1,3-butadiene

Organisation	US EPA	TCEQ	OEHHA
Year	2002	2008	2013
TRV	RfC	ReVc	REL
Value of the TRV	1.9 µg·m^{-3}	33 µg·m^{-3}	2.2 µg·m^{-3}
Critical effect	Ovarian atrophy	Ovarian atrophy	Ovarian atrophy
LOAEC	14 mg·m^{-3}	14 mg·m^{-3}	14 mg·m^{-3}
Species	Mice	Mice	Mice
Route of exposure	Inhalation (whole body)	Inhalation (whole body)	Inhalation (whole body)
Duration of exposure	2 years	2 years	2 years
Critical dose	$BMC_{10}L_{95}$ = Not indicated	BMC_5L_{95} = 1.04 mg·m^{-3}	BMC_5L_{95} = 2.27 mg·m^{-3}
Adjustments	Temporal adjustment = 6/24 x 5/7 Allometric adjustment (= 1) $BMC_{10}L_{95\ ADJ\ HEC}$ = 1.9 mg·m^{-3}	No temporal adjustment Allometric adjustment (1) $BMC_5L_{95\ ADJ\ HEC}$ = 1.4 mg·m^{-3}	Temporal adjustment = 6/24 x 5/7 Allometric adjustment (DAF = 1.68) $BMC_{10}L_{95\ ADJ\ HEC}$ = 0.67 mg·m^{-3}
UF	UF = 1000 UF_A = 3 (UF_{A-TK} = 1; UF_{A-TD} = 3) UF_H = 10 $UF_{B/L}$ = 10 UF_D = 3	UF = 30 UF_A = 1 (UF_{A-TK} = 0.3; UF_{A-TD} = 3) UF_H = 10 $UF_{B/L}$ = 1 UF_D = 3	UF = 300 UF_A = 10 (UF_{A-TK} = 1; UF_{A-TD} = 10) UF_H = 30 (UF_{H-TK} = 10; UF_{A-TD} =√10) $UF_{B/L}$ = 1 UF_D = 1
Source study	NTP (1993)	NTP (1993)	NTP (1993) Doerr *et al.* (1996)

BMC_xL_{95}: lower limit of the 95% confidence interval of the concentration leading to a x% increase in risk.
TRV: toxicity reference value; RfC: reference concentration; ReVc: chronic reference value, REL: reference exposure level
UF: uncertainty factor; UF_A: inter-species uncertainty factor (TK: toxicokinetic component; TD: toxicodynamic component); UF_D: database uncertainty factor; UF_H: inter-individual uncertainty factor
NTP: National Toxicology Program

In all three cases, the critical effect was ovarian atrophy. The TRV derived by the TCEQ was not selected since the methodology used is very different from that recommended by ANSES, in terms of adjustment and choice of uncertainty factors.

Between the approaches of the US EPA and OEHHA, which ultimately propose the same TRV value, the one adopted by OEHHA seems more consistent with ANSES's methodology with regard to the use of a PBPK model for allometric adjustment. However, the uncertainty factors chosen by OEHHA differ from ANSES's recommendations. Therefore, the **CES did not accept OEHHA's TRV as is, but selected the $BMC_{05}L_{95\ ADJ\ HEC}$[5] of 0.67 mg·m^{-3} as the critical dose. This value takes temporal and allometric adjustments into account.**

The TRV was calculated from the $BMC_{05}L_{95ADJ\ HEC}$ using an overall uncertainty factor of 300 broken down as follows (ANSES 2017):

- Inter-species variability: the UF_A was divided into two components – a toxicokinetic component (UF_{A-TK}) and a toxicodynamic component (UF_{A-TD}).

[5] human equivalent concentration of the lower limit of the 5% confidence interval of the concentration leading to a 10% increase in the risk of ovarian atrophy (after allometric adjustment)

- A UF_{A-TK} of 1 as proposed by OEHHA was selected, since allometric adjustment was performed.

- A UF_{A-TD} of 10 was selected by OEHHA based on humans being more susceptible than mice to the ovotoxicity. Even though this value is not consistent with ANSES's methodology, the CES considers it can be justified considering the risk of early menopause without prior evidence of disrupted menstrual cycles following chronic exposure to low concentrations of a substance affecting the preantral follicles (Mark-Kappeler *et al.,* 2011).

- Inter-individual variability: a UF_H of 30 was chosen by OEHHA to take genetic polymorphism into account. This approach is not consistent with ANSES's methodology, which recommends using a factor of 1, 3 or 10 to take interindividual variability into account. The CES therefore recommends using a factor of 10 for interindividual variability. This factor can also be corroborated by the model of Wallace & Kelsey (2010) on changes in the ovarian follicles from conception to menopause. A factor of 8.5 was noted between women born with a low number of follicles (2.5^{th} percentile) and women having an average-sized follicle population (Kirman *et al.,* 2012). Therefore, the factor of 10 would protect a sub-population of women particularly susceptible to ovotoxicity.

- Inadequacy of the database (UF_D): the CES recommends adding a UF_D of 3 to take into account the lack of data from investigations into potential reproductive toxicity and developmental neurotoxicity.

- Proposed TRV and confidence level

TRV = 2 µg·m^{-3} (rounded)

A **moderate-high** overall confidence level was assigned to this TRV based on the following four criteria: nature and quality of the data (moderate confidence level), choice of the critical effect and the mode of action (moderate confidence level), choice of the key study (high confidence level) and choice of the critical dose (high confidence level).

■ **Carcinogenic TRV by the respiratory route**

- Choice of the critical effect

The carcinogenic potential of 1,3-butadiene in humans has mainly been assessed based on epidemiological studies undertaken in workers in the synthetic rubber (styrene-butadiene) industry or producing butadiene monomer. These studies enabled a causal relationship to be established between mortality from leukaemia and exposure to 1,3-butadiene, based in particular on Delzell's cohort study. However, the CES considers that leukaemia as a whole is not an acceptable pathological entity. Therefore, **lymphoid tumours**, for which a statistically significant association with occupational exposure has been found according to Sielken *et al.*, **should be considered as the critical effect**.

- Establishment assumptions

There is strong evidence that the carcinogenicity mechanism is related to genotoxicity mediated by epoxide metabolites. **The CES therefore adopted a non-threshold approach for establishing a carcinogenic TRV by inhalation for 1,3-butadiene.**

- Analysis of the existing TRVs

Five organisations have established URs by the respiratory route: Health Canada (2000), the US EPA (2002), the TCEQ (2008), OEHHA (2013) and the BAuA (2015). In 2015, Sielken *et al.,* mandated by the TCEQ, also derived URs (see

Table 2).

The CES noted various limitations relating to:

- Choice of the critical effect: Health Canada, the US EPA and the TCEQ selected all types of leukaemia as the critical effect whereas Sielken *et al.* proposed URs for various sub-types of malignant blood diseases. The CES did not want to consider leukaemia as a whole because leukaemia encompasses a set of diseases that do not affect the same cell lines and have different risk factors. Moreover, all of the available URs are based on the data from the "Delzell" cohort study investigating cancer mortality, not incidence. Using mortality instead of incidence data can cause an underestimation of the risk. Therefore, to take these differences into account, the US EPA derived a TRV from the mortality data of the "Delzell" cohort study and from leukaemia incidence data for the United States, assuming that the dose-response relationship was the same. This approach was nonetheless criticised by Teta *et al.* (2004) who concluded that it leads to a biased estimate of the UR.
- Choice of the key study: all of the URs were derived from the data of the occupational cohort study by Delzell *et al*. Whereas Health Canada and the US EPA took into account the data from the initial publication of Delzell *et al*. in 1996, the TCEQ used an update where the cohort had been monitored until 1998 with the publication by Cheng *et al.* (2007). Sielken *et al.* also relied on an updated study of the cohort through to 1998 based on the data of Sathiakumar *et al.* (2005) and Macaluso *et al.* (2004) for the estimation of exposure. It should be noted that the cohort study was last updated in 2009 (Sathiakumar *et al.,* 2019).
- Establishment method: the URs were derived using similar methods: the lifetable analysis to determine the point of departure followed by linear extrapolation to the origin. However, the establishment assumptions differed in terms of the choice of exposure duration and construction of the lifetable.

Therefore, in light of these limitations, various options were discussed by the CES. **None of the existing carcinogenic TRVs by the respiratory route were selected by the CES. Considering the various limitations and uncertainties associated with these TRVs, the CES decided to establish a new TRV based on the latest update of Delzell's cohort study conducted by Sathiakumar *et al.*, which should be published shortly. This report should be updated to that end.**

Table 2: Summary of the chronic non-threshold TRVs available for 1,3-butadiene

Organisation/ Authors	**Health Canada**	**US EPA**	**TCEQ**	**OEHHA**	**BAuA**	**Sielken *et al*. (2015)**		
TRV	UR	UR	UR	UR	DMEL	UR		
Value of the TRV	**$5.9 \cdot 10^{-6}$ ($\mu g \cdot m^{-3}$)$^{-1}$**	**$3 \cdot 10^{-5}$ ($\mu g \cdot m^{-3}$)$^{-1}$**	**$5.0 \cdot 10^{-7}$ ($\mu g \cdot m^{-3}$)$^{-1}$**	**$1.7 \cdot 10^{-4}$ ($\mu g \cdot m^{-3}$)$^{-1}$**	**$6.7 \cdot 10^{-6}$ ($\mu g \cdot m^{-3}$)$^{-1}$**	**$1.2 \cdot 10^{-8}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (CLL)**	**$7.6 \cdot 10^{-8}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (lymphoid tumours)**	**$5.3 \cdot 10^{-8}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (total leukaemia)**[6]
Concentrations associated with several levels of risk	10^{-6}: 0.17 $\mu g \cdot m^{-3}$ 10^{-5}: 1.7 $\mu g \cdot m^{-3}$ 10^{-4}: 17 $\mu g \cdot m^{-3}$	10^{-6}: 0.03 $\mu g \cdot m^{-3}$ 10^{-5}: 0.3 $\mu g \cdot m^{-3}$ 10^{-4}: 3 $\mu g \cdot m^{-3}$	10^{-6}: 2 $\mu g \cdot m^{-3}$ 10^{-5}: 20 $\mu g \cdot m^{-3}$ 10^{-4}: 200 $\mu g \cdot m^{-3}$	10^{-6}: 0.006 $\mu g \cdot m^{-3}$ 10^{-5}: 0.06 $\mu g \cdot m^{-3}$ 10^{-4}: 0.6 $\mu g \cdot m^{-3}$	10^{-6}: 0.15 $\mu g \cdot m^{-3}$ 10^{-5}: 1.5 $\mu g \cdot m^{-3}$ 10^{-4}: 15 $\mu g \cdot m^{-3}$	10^{-6}: 83.3 $\mu g \cdot m^{-3}$ 10^{-5}: 833 $\mu g \cdot m^{-3}$ 10^{-4}: 8330 $\mu g \cdot m^{-3}$	10^{-6}: 13.16 $\mu g \cdot m^{-3}$ 10^{-5}: 131.6 $\mu g \cdot m^{-3}$ 10^{-4}: 1316 $\mu g \cdot m^{-3}$	10^{-6}: 188 $\mu g \cdot m^{-3}$ 10^{-5}: 1876 $\mu g \cdot m^{-3}$ 10^{-4}: 18900 $\mu g \cdot m^{-3}$
Duration of exposure considered for human data	Exp: 70 years	Exp: 85 years	Exp: 70 years		Exp: 70 years	Exp: 70 years		
						$4.9 \cdot 10^{-8}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (CLL)	**$2.2 \cdot 10^{-7}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (lymphoid tumours)**	**$1.5 \cdot 10^{-7}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (total leukaemia)**[7]
						10^{-6}: 20.25 $\mu g \cdot m^{-3}$ 10^{-5}: 202.5 $\mu g \cdot m^{-3}$ 10^{-4}: 2025 $\mu g \cdot m^{-3}$	10^{-6}: 4.5 $\mu g \cdot m^{-3}$ 10^{-5}: 45 $\mu g \cdot m^{-3}$ 10^{-4}: 450 $\mu g \cdot m^{-3}$	10^{-6}: 6.75 $\mu g \cdot m^{-3}$ 10^{-5}: 67.5 $\mu g \cdot m^{-3}$ 10^{-4}: 675 $\mu g \cdot m^{-3}$
						Exp: 85 years		
Year	2000 (2017)	2002	2009	2011	2015	2015		
Critical effect	Mortality from leukaemia	Mortality from leukaemia	Mortality from leukaemia	Pulmonary tumours	Mortality from leukaemia	Mortality from chronic lymphocytic leukaemia; lymphoid tumours; total leukaemia		
Species	Humans	Humans	Humans	Mice	Humans	Humans		
Exposure type	Occupational	Occupational	Occupational	Experimental	Occupational	Occupational		
Route of exposure	Inhalation	Inhalation	Inhalation	Inhalation	Inhalation	Inhalation		
Establishment Adjustments Extrapolation to low concentrations	Duration of exposure considered: 70 years Poisson modelling Lifetable (mortality) TC_{01} estimation	Duration of exposure considered: 85 years Poisson modelling Lifetable (incidence)	Duration of exposure considered: 70 years Cox modelling Lifetable (mortality)	LMS model	Duration of exposure considered: 70 years Adjustment of the value derived by the AGS (2008) for workers to take differences	Duration of exposure considered: 70 and 85 years Cox modelling Survival tables (mortality) Linear extrapolation to the origin		

[6] Values corrected compared to the publication after exchanges with the authors.
[7] Value not corrected *a priori*, taken from Table 5 of the publication

Organisation/ Authors	Health Canada	US EPA	TCEQ	OEHHA	BAuA	Sielken *et al*. (2015)
	$0.01/TC_{01}$	Linear extrapolation to the origin Adjustment of the excess risk due to potential underestimation of the risk (factor of 2)	Linear extrapolation to the origin		in exposure into account	
Source study	Delzell *et al.* (1996)	Delzell *et al.* (1996); Health Canada (1998)	Cheng *et al.* (2007)	Melnick *et al.* (1990)	Not specified	Sathiakumar *et al.* 2005 Macaluso *et al.,* 2004

AGS: *Ausschuss für Gefahrstoffe*; TC: tumorigenic concentration; DMEL: derived minimal-effect level; LMS: linearised multistage
CLL: chronic lymphocytic leukaemia
BAuA: *Bundesanstalt für Arbeitsschutz und Arbeitsmedizin*

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions and recommendations of the CES on "Health reference values" on the establishment of TRVs by the respiratory route for 1,3-butadiene.

Table 3: Chronic TRV by the respiratory route for 1,3-butadiene

Type of TRV	Critical effect (key study)	Critical concentration	UF	TRV
Chronic TRV by the respiratory route	Ovarian atrophy NTP (1993): two-year study in mice	$BMC_{05}L_{95}$ = 2.27 mg·m^{-3} Temporal adjustment $BMC_{05}L_{95\ ADJ}$ = $BMC_{05}L_{95}$ x 6/24 x 5/7 = 0.41 mg·m^{-3} Allometric adjustment (HEC where DAF = 1.68) $BMC_{05}L_{95\ ADJ\ HEC}$ = 0.67 mg·m^{-3}	300 UF_{A-TK} = 1 UF_{A-TD} = 10 UF_H = 10 $UF_{B/L}$ = 1 UF_D = 3	**2 µg·m^{-3}** **Confidence level: moderate-high**

Due to the uncertainties associated with the existing carcinogenic TRVs, ANSES recommends establishing a new non-threshold TRV based on the most recent update of the cohort study by Delzell *et al.* that should be published shortly.

Moreover, the US EPA is currently revising its risk assessment of 1,3-butadiene; the revised version should be published in 2023.

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MOTS-CLES

Valeur toxicologique de référence, VTR, 1,3-butadiène, chronique, inhalation, seuil, sans seuil, cancer

KEYWORDS

Toxicity reference value, TRV, 1,3-butadiene, chronic, inhalation, threshold, non-threshold, cancer