**ANSES Opinion**
**Request No 2019-SA-0073**

The Director General

Maisons-Alfort, 6 November 2023

# Revised OPINION[1]
## 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)**

*ANSES undertakes independent and pluralistic scientific expert assessments.*
*ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.*
*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 6 November 2023 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 chronic toxicity reference values (TRVs) by the respiratory route 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;

[1] Cancels and replaces the opinion of 17 October 2022 (see change history in Annex 1).

- choosing a good-quality scientific study generally enabling a dose-response relationship to be established;
- defining a point of departure (PoD) for humans or animals from this study and, if required, in the case of a PoD obtained in animals, adjusting this dose to humans;
- for a threshold TRV, applying uncertainty factors to this PoD 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 a unit risk (UR).

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.

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) was most frequently used (US EPA, 2002). 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 (INERIS, 2011: OEHHA, 2013). Since then, new studies have been published and a new carcinogenic TRV has been established by the Texas Commission on Environmental Quality (TCEQ) in 2008 but published with free access in 2013 (TCEQ, 2015). 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.

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).

ANSES issued an initial opinion in January 2021, proposing a chronic threshold TRV by inhalation. Although carcinogenicity had already been included in the toxicological profile of this substance, the critical analysis of the TRVs proposed by other reference organisations did not enable a non-threshold TRV to be adopted. The Agency recommended establishing a non-threshold TRV based on the updated "Delzell" cohort study, which had yet to be published. This new opinion is therefore supplementing the one of January 2021 to propose a non-threshold carcinogenic TRV by inhalation as recommended.

## 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 for the toxicological profile and the proposal of a chronic threshold TRV, and between November 2021 and June 2022 for the establishment of a carcinogenic TRV. The work was adopted by the CES on 30 June 2022.

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

### 3.1. 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 2008-2021 period (see Annex 3 of the report). In connection with the background of the request, the analysis focused on the observed toxic effects following a chronic exposure by inhalation.

#### 3.1.1. 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) (see Figure 1). However, there are quantitative differences in the kinetics of 1,3-butadiene depending on the species. For example, the oxidation rate (Vmax/Km)[2] 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.

[2] Maximum velocity/Michaelis constant

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).

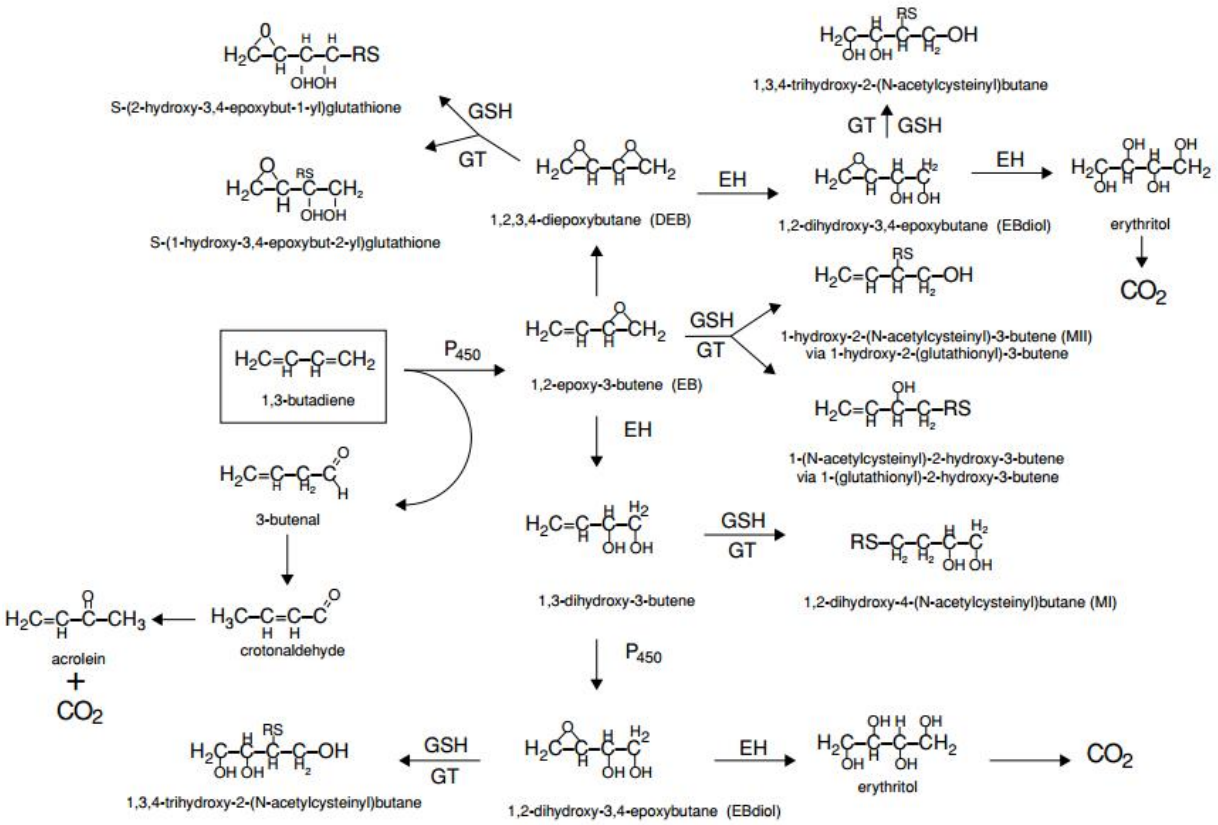


**Figure 1: Diagram representing the metabolism of 1,3-butadiene (adapted from Health Canada, 2000)**

### 3.1.2. Acute effects

$LC_{50}$[3] 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).

### 3.1.3. Subchronic and chronic effects

Some epidemiological data have shown 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.

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

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 cytolysis, 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 study in mice, the critical effect was ovarian atrophy, whose incidence significantly increased at all the tested concentrations (NTP, 1993). Examination of these results led the CES to propose a LOAEC[4] of 14 $mg \cdot m^{-3}$ for these effects.

#### 3.1.4. Effects on reproduction and development

No OECD[5] guideline studies for analysing effects on fertility 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 $mg \cdot m^{-3}$) (NTP, 1983). 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).

#### 3.1.5. 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).

#### 3.1.6. 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.

- Data in humans

The available epidemiological data come from studies in occupational cohorts of workers in the synthetic rubber (styrene-butadiene) industry or producing butadiene monomer. These studies assessed the relationship between the occurrence of tumours and exposure to 1,3-butadiene.
The largest cohort study on workers from the butadiene monomer production industry was the one initiated by Downs *et al*. in the United States in 1987 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-

[4] Lowest Observed Adverse Effect Concentration

[5] Organisation for Economic Co-operation and Development

Hodgkin's lymphoma) (SMR[6] = 141; $CI_{95\%}$[7] = 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 that initiated by Delzell *et al.* in 1996 and then regularly updated (it was last updated in 2009; Sathiakumar *et al.,* 2019 and 2021). This multi-centre retrospective cohort study, known as the "Delzell" cohort study, initially included 15,649 (male) workers spread out across eight North American sites (in Canada and the USA). As the study was updated, mortality was monitored over a longer period. Exposure estimates relied on job-exposure matrices using company archives, tasks and processes in use over time, and atmospheric measurements taking distances and means of protection 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 analysed, thus leading noncomparable diseases to be grouped together. The three most recent studies of Sathiakumar *et al*. (2015, 2019 and 2021) presented the most complete analyses. Several earlier articles had been published on the monitoring of this cohort, but only these last three studies included health data updated through to 2009. In the 2019 publication, a statistically significant increase in deaths was observed for all types of leukaemia, including lymphoid and myeloid leukaemia (SMR = 139; $CI_{95\%}$ = 106-179) and non-Hodgkin's lymphoma (NHL) (SMR = 136; $CI_{95\%}$ = 102-177), for the sub-group of employees paid by the hour at a given time in their career, who had been occupationally exposed for at least 10 years and employed for more than 20 years. The Cox regression analysis of cumulative exposure as a continuous 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 in the authors' analyses. The main limitations of the analysis of this cohort study's data were its inability to take into account certain confounding factors such as smoking and its use of mortality instead of incidence (in particular considering that some cancers, including specific forms of leukaemia, can be associated with a long survival time).

In 2021, Sathiakumar's team carried out an additional study, following on from its last two studies (Sathiakumar *et al*., 2015 and 2019), focusing on lymphoid and haematopoietic diseases (Sathiakumar *et al*., 2021). The cohort consisted of 17,924 men and 4,861 women, employed between 1943 and 1 January 1992, for at least one year for the men and at least one day for the women. The analyses focused on 21,087 employees, including 66% who had been exposed to 1,3-butadiene (median = 48 ppm-years, mean = 187 ppm-years) and 73% to styrene (median = 11 ppm-years, mean = 38 ppm-years). Deaths related to the diseases of interest were as follows: 132 from leukaemia (all forms combined), 52 from lymphoid leukaemia, 67 from myeloid leukaemia, 41 from acute myeloid leukaemia (AML), 110 from NHL, and 60 from multiple myeloma.

The new analysis of the same data again tested the dose-response relationship with cumulative exposure to 1,3-butadiene and styrene, but for the entire cohort (21,087 people). Regarding "leukaemia", the restricted cubic spline (RCS) analyses performed by the authors showed a linear increase in the risk with cumulative exposure to 1,3-butadiene up to 1000 ppm-years, after which the curve flattened. The relative risk (RR) for the upper quartile was 2.53 ($CI_{95\%}$ = 1.37-4.67). Concerning "lymphoid leukaemia", the results of the analysis were fairly similar to those reported for "leukaemia" as a whole: the RR was 2.61 ($CI_{95\%}$ = 1.02-6.67) for the 3$^{rd}$ quartile and 1.95 ($CI_{95\%}$ = 0.76-5.03) for the 4$^{th}$ quartile of cumulative exposure to 1,3-butadiene (p-trend = 0.007). This study confirmed the results of the two previous studies: there was a positive association between cumulative exposure to 1,3-butadiene and the risk of death from "leukaemia" and "lymphoid leukaemia" in this cohort.

[6] Standardised mortality ratio

[7] 95% confidence interval

Several authors have investigated the role of environmental exposure to various pollutants, including 1,3-butadiene, in the occurrence of various types of cancer in children.
1,3-butadiene has been associated with an increased risk of leukaemia as defined in the 10th version of the International Classification of Diseases (ICD) of the World Health Organization, dating from 2016 (ICD-10 C91-95). This was based on the results of an ecological study carried out by Whitworth *et al*. (2008). An association between 1,3-butadiene as an air pollutant and the risk of acute (lymphoid and/or myeloid) leukaemia in childhood was also reported in a meta-analysis undertaken by Filippini *et al*. (RR = 1.45; $CI_{95\%}$ = 1.08-1.95 – based on two studies including 1,3-butadiene) (Filippini *et al*., 2019).
Von Ehrenstein *et al*. examined the risk of developing brain tumours in children following *in utero* and early childhood exposure to air pollutants, including 1,3-butadiene (Von Ehrenstein *et al*., 2016). Cases of central nervous system primitive neuroectodermal tumours (≤ 38) diagnosed in children under six years of age extracted from the California Cancer Registry between 1990 and 2007 were positively associated with various pollutants, including 1,3-butadiene (odds ratio (OR) = 2.23; $CI_{95\%}$ = 1.28-3.88).
A case-control study, including 243 cases of germ cell tumours in children under the age of six, reported an increased risk of this type of tumour (in particular yolk sac tumours) with exposure to air pollutants, including 1,3-butadiene (OR = 1.51; $CI_{95\%}$ = 1.01-2.26), during the second trimester of pregnancy (Hall *et al.*, 2019).

- Animal data

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).

## 3.2. Chronic threshold TRV by the respiratory route

### 3.2.1. 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[8] studies at higher concentrations. The US EPA suggested that uterine atrophy may be due to a decrease in oestrogen caused by ovarian atrophy (US EPA, 2002). It seems that the testicles are less susceptible to the toxic effects of 1,3-butadiene than the ovaries.

[8] National Toxicology Program

### 3.2.2. 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** | **Name** | RfC | ReVc | REL |
| | **Value** | 1.9 µg·m$^{-3}$ | 33 µg·m$^{-3}$ | 2.2 µg·m$^{-3}$ |
| **Critical effect** | | Ovarian atrophy | | |
| **Source study** | **Reference** | NTP (1993) | | NTP (1993); Doerr *et al.* (1996) |
| | **Species** | Mice | | |
| | **Exposure** | Inhalation (whole body) | | |
| **PoD** | | LOAEC = 14 mg·m$^{-3}$<br>$BMC_{10}L_{95}$ = Not indicated | LOAEC = 14 mg·m$^{-3}$<br>$BMC_5L_{95}$ = 1.04 mg·m$^{-3}$ | LOAEC = 14 mg·m$^{-3}$<br>$BMC_5L_{95}$ = 2.27 mg·m$^{-3}$ |
| **Adjustments** | **Temporal** | $BMC_{10}L_{95\ ADJ}$ = 6/24 x 5/7 | No temporal adjustment | = 6/24 x 5/7 |
| | **Allometric** | (= 1)<br>$BMC_{10}L_{95\ ADJ\ HEC}$ = 1.9 mg·m$^{-3}$ | (= 1)<br>$BMC_5L_{95\ ADJ\ HEC}$ = 1.4 mg·m$^{-3}$ | (DAF = 1.68)<br>$BMC_{10}L_{95\ ADJ\ HEC}$ = 0.67 mg·m$^{-3}$ |
| **UF** | | UF = 1000<br>$UF_A$ = 3 ($UF_{A\text{-}TK}$ = 1; $UF_{A\text{-}TD}$ = 3)<br>$UF_H$ = 10<br>$UF_{B/L}$ = 10<br>$UF_D$ = 3 | UF = 30<br>$UF_A$ = 1 ($UF_{A\text{-}TK}$ = 0,3; $UF_{A\text{-}TD}$ = 3)<br>$UF_H$ = 10<br>$UF_{B/L}$ = 1<br>$UF_D$ = 3 | UF = 300<br>$UF_A$ = 10 ($UF_{A\text{-}TK}$ = 1; $UF_{A\text{-}TD}$ = 10)<br>$UF_H$ = 30 ($UF_{H\text{-}TK}$ = 10; $UF_{A\text{-}TD}$ =√10)<br>$UF_{B/L}$ = 1<br>$UF_D$ = 1 |

$BMC_xL_{95}$: 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 (ANSES, 2017).

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 human equivalent concentration of the lower limit of the 95% confidence interval of the concentration leading to a 10% increase in the risk of ovarian atrophy after allometric adjustment ($BMC_{05}L_{95\ ADJ\ HEC}$) of 0.67 mg·m$^{-3}$ as the PoD to establish the chronic TRV. 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 ($UF_{A\text{-}TK}$) and a toxicodynamic component ($UF_{A\text{-}TD}$):
    - A $UF_{A\text{-}TK}$ of 1 as proposed by OEHHA was selected, since allometric adjustment was performed;
    - A $UF_{A\text{-}TD}$ of 10 was selected by OEHHA based on humans being more susceptible than mice to the ovarian toxicity. 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 ovarian toxicity;

- 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.

#### 3.2.3. Proposed TRV and confidence level

TRV = 2 $\mu g \cdot m^{-3}$ (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).

### 3.3. Carcinogenic TRV by the respiratory route

#### 3.3.1. Choice of the critical effect

1,3-butadiene is classified as a Group 1 carcinogen (carcinogenic to humans) by the International Agency for Research on Cancer (IARC, 2008, 2012) and as a Category 1A carcinogen (may cause cancer) in Europe under the CLP Regulation.
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 relationship to be established between mortality from leukaemia (all types combined) and lymphoid leukaemia and exposure to 1,3-butadiene, based in particular on the “Delzell” cohort. However, the CES considers that leukaemia as a whole is not an acceptable disease entity given that, in the current state of knowledge and according to the current classifications of haematological diseases, the term "leukaemia" refers to a heterogeneous group of diseases that affect different haematopoietic and lymphatic tissues and do not have the same risk factors.
**Therefore, the CES selected lymphoid leukaemia as a whole as the critical effect**, for which a statistically significant association with occupational exposure to 1,3-butadiene was found in the “Delzell” cohort study (Sathiakumar *et al.*, 2019 and 2021).

#### 3.3.2. Establishment assumptions

There is strong evidence that the carcinogenicity mechanism is related to genotoxicity mediated by epoxide metabolites. **The CES concluded that 1,3-butadiene and its metabolites have genotoxic effects (gene mutations, deletions, etc.) and that these effects show a non-threshold dose-response relationship.**

#### 3.3.3. Analysis of the existing TRVs

**Five organisations have established URs by the respiratory route: Health Canada (2000), the US EPA in 2002, the TCEQ in 2008, OEHHA in 2013 and the BAuA[9] in 2015. In 2015, Sielken *et al.,* mandated by the TCEQ, also derived URs (Sielken *et al*., 2015) (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. As stated above, 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.* who concluded that it leads to a biased estimate of the UR (Teta *et al.,* 2004).

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.* in 2007. Sielken *et al.* also relied on an updated study of the cohort through to 1998 based on the data of Sathiakumar *et al.* and Macaluso *et al.* for the estimation of exposure (Sathiakumar *et al.*, 2005; Macaluso *et al.,* 2004). 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 PoD 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, the CES did not adopt the existing carcinogenic TRVs by the respiratory route, considering their various limitations and uncertainties, and suggested establishing a new TRV.**

[9] German Federal Institute for Occupational Safety and Health (Bundesanstalt für Arbeitsschutzund Arbeitsmedizin)

**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) | | |
|---|---|---|---|---|---|---|---|---|---|
| Year | | 2000 (2017) | 2002 | 2009 | 2011 | 2015 | 2015 | | |
| TRV | Name | UR | UR | UR | UR | DMEL | UR | | |
| | Value of the TRV<br><br>Concentrations associated with several levels of risk<br><br>Duration of exposure considered for human data | **$5.9 \cdot 10^{-6}$ ($\mu g \cdot m^{-3}$)$^{-1}$**<br><br>$10^{-6}$: 0.17 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 1.7 $\mu g \cdot m^{-3}$<br>$10^{-4}$: 17 $\mu g \cdot m^{-3}$<br><br>Exp: 70 years | **$3 \cdot 10^{-5}$ ($\mu g \cdot m^{-3}$)$^{-1}$**<br><br>$10^{-6}$: 0.03 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 0.3 $\mu g \cdot m^{-3}$<br>$10^{-4}$: 3 $\mu g \cdot m^{-3}$<br><br>Exp: 85 years | **$5.0 \cdot 10^{-7}$ ($\mu g \cdot m^{-3}$)$^{-1}$**<br><br>$10^{-6}$: 2 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 20 $\mu g \cdot m^{-3}$<br>$10^{-4}$: 200 $\mu g \cdot m^{-3}$<br><br>Exp: 70 years | **$1.7 \cdot 10^{-4}$ ($\mu g \cdot m^{-3}$)$^{-1}$**<br><br>$10^{-6}$: 0,006 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 0.06 $\mu g \cdot m^{-3}$<br>$10^{-4}$: 0.6 $\mu g \cdot m^{-3}$ | **$6.7 \cdot 10^{-6}$ ($\mu g \cdot m^{-3}$)$^{-1}$**<br><br>$10^{-6}$: 0.15 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 1.5 $\mu g \cdot m^{-3}$<br>$10^{-4}$: 15 $\mu g \cdot m^{-3}$<br><br>Exp: 70 years | **$1.2 \cdot 10^{-8}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (CLL)**<br><br>$10^{-6}$: 83.3 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 833 $\mu g \cdot m^{-3}$<br>$10^{-4}$: 8330 $\mu g \cdot m^{-3}$<br><br>Exp: 70 years<br><br>**$4.9 \cdot 10^{-8}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (CLL)**<br><br>$10^{-6}$: 20.25 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 202.5 $\mu g \cdot m^{-3}$<br>$10^{-4}$: 2025 $\mu g \cdot m^{-3}$<br><br>Exp: 85 years | **$7.6 \cdot 10^{-8}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (lymphoid tumours)**<br><br>$10^{-6}$: 13.16 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 131.6 $\mu g \cdot m^{-3}$<br>$10^{-4}$: 1316 $\mu g \cdot m^{-3}$<br><br>**$2.2 \cdot 10^{-7}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (lymphoid tumours)**<br><br>$10^{-6}$: 4.5 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 45 $\mu g \cdot m^{-3}$<br>$10^{-4}$: 450 $\mu g \cdot m^{-3}$ | **$5.3 \cdot 10^{-8}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (total leukaemia)***<br><br>$10^{-6}$: 188 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 1876 $\mu g \cdot m^{-3}$<br>$10^{-4}$: 18900 $\mu g \cdot m^{-3}$<br><br>**$1.5 \cdot 10^{-7}$ ($\mu g \cdot m^{-3}$)$^{-1}$ (total leukaemia)****<br><br>$10^{-6}$: 6.75 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 67.5 $\mu g \cdot m^{-3}$<br>$10^{-4}$: 675 $\mu g \cdot m^{-3}$ |
| 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 | | |
| Source study | Reference | 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<br>Macaluso *et al.,* 2004 | | |
| | Species | Humans | Humans | Humans | Mice | Humans | Humans | | |
| | Exposure | Occupational Inhalation | Occupational Inhalation | Occupational Inhalation | Experimental Inhalation | Occupational Inhalation | Occupational Inhalation | | |
| Establishment<br><br>Adjustments<br><br>Extrapolation to low concentrations | | Duration of exposure considered: 70 years<br>Poisson modelling<br>Lifetable (mortality)<br>$TC_{01}$ estimation<br>0.01/$TC_{01}$ | Duration of exposure considered: 85 years<br>Poisson modelling<br>Lifetable (incidence)<br>Linear extrapolation to the origin<br><br>Adjustment of the excess risk due to potential underestimation of the risk (factor of 2) | Duration of exposure considered: 70 years<br>Cox modelling<br>Lifetable (mortality)<br>Linear extrapolation to the origin | LMS model | Duration of exposure considered: 70 years<br>Adjustment of the value derived by the AGS (2008) for workers to take differences in exposure into account | Duration of exposure considered: 70 and 85 years<br>Cox modelling<br>Survival tables (mortality)<br>Linear extrapolation to the origin | | |

* Values corrected compared to the publication after exchanges with the authors; ** Value not corrected a priori, taken from Table 5 of the publication; 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*

## 3.4. Establishment of the non-threshold TRV

### 3.4.1. Choice of the key study

According to ANSES's method for establishing TRVs (ANSES, 2017), good-quality data in humans are preferred to data obtained from animals.
The critical effect selected was "lymphoid leukaemia" as a whole. According to the interview with Sathiakumar et al., the entities encompassed by the term "lymphoid leukaemia" used in their article correspond to Code 204 of the WHO's ICD classification of malignant blood diseases between 1958 and 1998 and to Code C91 of the newer versions of this same classification from 1999 onwards (see the list of diseases included in C91 in Annex 4 of the report).
Quantitatively speaking, the main disease covered by Code C91 is chronic lymphoid leukaemia (CLL) (incidence: 2 to 4 per 100,000 person-years). The only other blood disease in Code C91 of the same order of frequency (incidence: 1 to 2 per 100,000 person-years) is acute lymphoblastic leukaemia (ALL). However, ALL is mainly a childhood disease: 50% of cases occur before the age of 18 and the start of working life. In the absence of an incidence study, the CES selected a mortality study that demonstrated a significant link between mortality from lymphoid leukaemia and exposure to 1,3-butadiene in humans. The study by Sathiakumar et al. in 2021, which was an analysis of the updated data from the "Delzell" cohort, was deemed to be of good quality because it had a long follow-up period (1943-2009) and assessed exposure to 1,3-butadiene independently of self-reports (use of a job-exposure matrix). This study showed an increased risk of death from "lymphoid leukaemia" associated with exposure to 1,3-butadiene.
**Therefore, the CES chose the study by Sathiakumar *et al*. (2021) as the key study.**

### 3.4.2. Establishing the UR

A unit risk (UR) is the excess risk of an adverse health effect occurring in individuals exposed to an exposure concentration unit in their lifetime or working life, compared with unexposed individuals. The UR is calculated from the excess lifetime risk (ELR). It corresponds to the slope obtained by linear extrapolation to the origin of the curve representing the ELR when the concentrations in the epidemiological study are higher than the concentrations in the environment.

### 3.4.3. Approach adopted

Two approaches have traditionally been used to express the ELR for various levels of exposure. These approaches can be applied using the concentration-risk functions reported in the key epidemiological study:

- **a "simple" approach** using the probability P of the critical effect occurring in an unexposed population,
- **a cumulative-risk approach** based on the use of lifetables[10] or incidence tables; this involves subtracting the cumulative lifetime risk of the critical effect in the unexposed population from that in the exposed population.

The ELR established using the lifetable approach is considered more accurate than that obtained using the simple approach. This is because lifetables allow for the calculation of probabilities

[10] A lifetable (or mortality table) shows the conditional probability that a health event will occur, by age group (and sometimes by gender), within a real or fictitious population (Goldbohm *et al*., 2006; Steenland *et al*., 1998; Vaeth and Pierce, 1990; van den Brandt *et al*., 2002). This probability is said to be conditional because it is the likelihood of the event of interest (or critical effect) occurring subject to the survival of the individuals from one age group to the next. It was initially based on mortality data, but can also be used with incidence data, with a few adaptations depending on the data available and the effects considered.
The lifetable approach has been used in particular to establish non-threshold TRVs characterising the occurrence of cancer as a function of exposure to a chemical substance or radionuclide, based on key epidemiological workplace studies (Goldbohm *et al*., 2006; ECHA, 2019; National Research Council, 1988; US EPA, 2002 and 2011).

conditional on survival from one age group to the next, taking account of potential competing risks[11] over a lifetime that are different from the health event of interest, i.e. risks linked to diseases or causes of death other than the one of interest. The lifetable approach should be favoured when the necessary data (incidence or mortality by age group in France for the critical effect) are available. **The CES therefore adopted the lifetable approach.**

Several assumptions should be made to support the use of a concentration-risk function to calculate an ELR. First of all, it is necessary to ensure that this function and the associated risk are applicable throughout a lifetime – or in any case, at the ages considered in the simple and cumulative-risk approaches. Next, the function from the epidemiological study should be considered applicable to the population targeted by the ELR calculation.

In human studies, lifetime risk is seldom directly observed. Nevertheless, epidemiological analyses of disease risk over shorter time periods can be used to calculate lifetime risk subject to certain assumptions:

1. the exposure-risk (disease or death) relationship is applicable at various ages (if there are not enough epidemiological data to provide age-specific exposure-risk relationships, empirical data can be used and no assumptions are then necessary);
2. the exposure-risk (disease or death) relationship observed in the epidemiological study is applicable to the target population.

The lifetable approach includes several successive calculation steps, enabling R0 and RX to be estimated for the calculation of the ELR:

1) R0 is the cumulative conditional lifetime probability of the critical effect occurring in an unexposed population – this is the lifetime baseline risk. A lifetime here corresponds to the range of age groups considered in the lifetable (from <1 to 84 years). Calculating R0 requires two types of primary data in the unexposed population that must be available by age group: the probability of death from all causes for individuals, and the probability of occurrence of the critical effect, in this case, lymphoid leukaemia;

2) RX is the cumulative conditional lifetime probability of the critical effect occurring in an exposed population. In addition to the data used and values calculated for R0, the calculation of RX uses the risk reported in an epidemiological study linking a level of exposure to the critical effect (i.e. a concentration-risk function). Exposure can be considered average or cumulative;

3) The ELR is calculated as an extra risk:

$$ELR = (RX-R0)/(1-R0)$$

CLL is a disease that progresses over long periods and only very rarely leads to death. It is therefore a condition for which a mortality study will be less likely than an incidence study to reflect the excess lifetime risk associated with exposure to 1,3-butadiene. The CES therefore adopted the adapted lifetable approach, which uses a lifetable combined with all-cause mortality data and incidence data

[11] A competing risk is a situation or event (other than the one of interest) that fundamentally impacts the probability of occurrence of the health event of interest (= critical effect). In this specific case, death – whatever the cause – is considered a competing risk.

for the critical effect (lymphoid leukaemia as a whole). The adaptation developed for 1,3-butadiene by the TCEQ in 2013 was used.

**In view of the critical effect selected (lymphoid leukaemia, especially CLL) and the difference between the incidence and mortality of CLL, the CES adopted the lifetable approach adapted for the use of incidence data, which uses a lifetable combined with all-cause mortality data and incidence data for the critical effect.**

- **Collection of health data for the lifetime baseline risk**

The ELR is calculated by projecting a concentration-risk function selected from the epidemiological literature onto the baseline risk of the critical health effect in the target population, denoted $R_0$ for the lifetable approach. The target population is the French population (metropolitan France and overseas territories).

Following discussions with Sathiakumar *et al*., the ICD codes for diseases used in this study were clarified to define "lymphoid leukaemia", in order to verify that the aggregations of malignant blood diseases performed were mechanistically acceptable. It was decided that the disease entities covered by the term "lymphoid leukaemia" in the article are all the diseases falling under ICD-10 Code C91 (from C91.0 to C91.9) (Annex 4 of the report).

For the incidence data collected from *Santé publique France* (SpF), the inventory of blood diseases includes 24 disease entities, three of which correspond to diseases falling under ICD-10 Code C91 (lymphoid leukaemia). These are as follows:

-32.01: chronic lymphoid leukaemia (corresponding to ICD-10 Code C91.1),
-32.09: hairy cell leukaemia (corresponding to ICD-10 Code C91.4),
-32.11: lymphoblastic leukaemia (corresponding to ICD-10 Code C91.0),

These three entities only correspond to three of the 10 subcategories of the ICD-10 C91 code, but quantitatively they account for the vast majority of the blood diseases associated with this code.

Numbers of deaths and crude all-cause mortality rates associated with the critical effect (Code C91) in an unexposed population in France were collected for males and females from the Epidemiology Centre on Medical Causes of Death (CépiDc – INSERM).

The data used to calculate R0 were mortality or incidence rates for the critical effect (Code C91 here) in an unexposed population in France. These were crude rates by age group from <1 year to 84 years, including males and females, for 2015, 2016 and 2017. These rates were collected from the data owners: CépiDc (INSERM) for mortality data and SpF for incidence data.

In order to use these data in the lifetable, the mortality data (CépiDc – INSERM) for 2015, 2016 and 2017 were averaged and weighted based on the numbers of males and females (numbers for France and for each age group).

The incidence data were calculated by weighting the predicted crude incidence rates (in person-years) for the disease in question, for each year in question and for each age group, and by averaging the weighted incidence rates for males and females.

- **Calculation of the ELR using the lifetable**

The ELR was calculated as an extra risk and required a preliminary calculation phase using the lifetable, which is available in Annex 5 of the report.

The risk was estimated using the RR estimated in the epidemiological study for lymphoid leukaemia (RR = 2.70; $CI_{95\%}$ = 1.08-6.76; β coefficient = $4.91.10^{-4}$; $CI_{95\%}$ = 1.51-8.31) and the adapted lifetable, which took into account competing causes of death, i.e. incidence rates for lymphoid leukaemia, as well as all-cause mortality rates by age group and for the French population not exposed to 1,3-butadiene.

When epidemiological data were used for cancer data in accordance with the US EPA guidelines (US EPA, 2005), the ELR was set at 1%.

The risk was calculated using a lifetable for continuous exposure to 1,3-butadiene up to the age of 84. The exposure observed in the epidemiological study was converted into continuous lifetime exposure by multiplying occupational exposure by a factor considering the number of days of exposure per year (365/240 days) and the difference in the amount of air inhaled per day between workers and the general population (20/10 $m^3$).

The PoD was calculated by considering the upper limit of the 95% confidence interval for the β regression coefficient (β = $4.91.10^{-4}$; $CI_{95\%}$ = 1.51-8.31) in accordance with the US EPA's guidelines and ANSES's practices. The UR calculated from the PoD of 6 ppm by linear extrapolation to the origin is given in the table below.

The corresponding UR expressed in $(ppm)^{-1}$ is then converted to $(\mu g.m^{-3})^{-1}$ using the following conversion factor (taken at 25°C and considering a molar volume of 24.05 L) 1 ppm of 1,3-butadiene is equal to 2212 $\mu g.m^{-3}$.

**Table 3: PoD, UR and concentrations associated with the various risk levels**

| PoD[1] | UR[2] | Concentrations for various risk levels |
|---|---|---|
| 6 ppm | 0.00167 $(ppm)^{-1}$ | $10^{-4}$: 0.06 ppm<br>$10^{-5}$: 0.006 ppm<br>$10^{-6}$: 0.0006 ppm |
| 13,272 $\mu g \cdot m^{-3}$ | $7.5 \cdot 10^{-7}$ $(\mu g \cdot m^{-3})^{-1}$ | $10^{-4}$: 133 $\mu g \cdot m^{-3}$<br>$10^{-5}$: 13 $\mu g \cdot m^{-3}$<br>$10^{-6}$: 1.3 $\mu g \cdot m^{-3}$ |

[1]PoD: calculated with the upper limit of the 95% confidence interval for the β regression coefficient and an ELR set at 1% [2]UR = 0.01/PoD

#### 3.4.4. Proposed TRV and confidence level

$$\mathbf{TRV = 7.5 \cdot 10^{-7} \ (\mu g \cdot m^{-3})^{-1}}$$

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

### 3.5. Conclusion and recommendations

Two chronic respiratory TRVs have been established for 1,3-butadiene:

- a chronic threshold TRV with a **moderate/high** confidence level,
- a non-threshold carcinogenic TRV with a **high** confidence level.

The chronic TRV for threshold-dose effects corresponds to a cancer risk below $10^{-6}$.

**Table 4: Chronic and carcinogenic TRVs by the respiratory route for 1,3-butadiene**

<table>
<tr><th>Type of TRV</th><th>Body establishing the value (date)</th><th>Critical effect (key study)</th><th colspan="2">Establishment</th><th>TRV</th></tr>
<tr><td rowspan="2">Chronic TRV by the respiratory route</td><td rowspan="2">ANSES (2021)</td><td rowspan="2">Ovarian atrophy<br><br>NTP (1993): two-year study in mice</td><td>PoD</td><td>UF</td><td rowspan="2">2 µg·m$^{-3}$</td></tr>
<tr><td>$BMC_5L_{95}$ = 2.27 mg·m$^{-3}$<br><br><u>Temporal adjustment</u><br>$BMC_5L_{95\ ADJ}$ = $BMC_5L_{95}$ = x 6/24 x 5/7 = 0.41 mg.m$^{-3}$<br><br><u>Allometric adjustment</u> (HEC where DAF = 1.68)<br>$BMC_5L_{95\ ADJ\ CEH}$ = 0.67 mg.m$^{-3}$</td><td>300<br><br>$UF_{A\text{-}TK}$ = 1<br>$UF_{A\text{-}TD}$ = 10<br>$UF_H$ = 10<br>$UF_{B/L}$ = 1<br>$UF_D$ = 3</td><td>Confidence level: moderate-high</td></tr>
<tr><td>Non-threshold carcinogenic TRV</td><td>ANSES (2022)</td><td>Lymphoid leukaemia (mortality)<br><br>Sathiakumar et al. (2021): epidemiological workplace study (exposure by inhalation)</td><td colspan="2">RR = 2.70 ($CI_{95\%}$ = 1.08-6.76), upper limit of the 95% confidence interval for the β coefficient = 8.31·10$^{-4}$<br><br>Incidence-adjusted lifetable with temporal adjustment<br><br>Linear extrapolation to the origin based on the PoD of 6 ppm for an ELR of 1%</td><td><b>UR = 7.5·10$^{-7}$ (µg·m$^{-3}$)$^{-1}$</b><br><br>For a risk of:<br>10$^{-4}$: 133 µg·m$^{-3}$<br>10$^{-5}$: 13 µg·m$^{-3}$<br>10$^{-6}$: 1.3 µg·m$^{-3}$</td></tr>
</table>

## 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.

The Agency reiterates that a toxicity reference value (TRV) is a toxicological indicator for qualifying or quantifying a risk to human health. TRVs enable the potential health effects of exposure to substances to be assessed. They can be used as part of quantitative health risk assessments (QHRAs) carried out at population level, in a given exposure context, and thus help in the choice of risk management measures. They can also be used to establish guidance values such as indoor air quality guidelines (IAQGs).

This opinion supplements the ANSES opinion of January 2021, which proposed a threshold TRV for 1,3-butadiene to protect against the chronic effects of exposure to this substance by inhalation, excluding carcinogenic effects. This additional opinion was expected and recommended by the Agency, given that the carcinogenicity of the substance is well established. As is customary, the TRV for a substance considered toxic without a dose threshold is expressed as a unit risk (UR), supplemented by the equivalent concentrations at different acceptable levels of individual excess risk (IER), conventionally from $10^{-4}$ to $10^{-6}$. The Agency emphasises that the concentration

associated with an IER of $10^{-6}$ established for chronic effects without a dose threshold is lower than the chronic threshold TRV, and is therefore more protective.

Pr Benoit Vallet

**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

## ANNEX 1: TRACKING OF OPINION UPDATES

| Date | Page(s) | Description of the change |
|---|---|---|
| July 2022 | Part 1 | Addition of an explanation on the revision of the opinion |
| | Part 2 | Updating of the organisation of the expert appraisal |
| | Part 3 | Summary of the toxicological data:<br>- revision of the section on carcinogenicity<br>- establishment of a carcinogenic TRV by inhalation<br>- conclusions and recommendations of the CES: revision |
| September 2022 | Part 4 | Revision of Part 4 |
| August 2023 | 15 | Revision of Table 3, section 3.4.3.<br>Revision of the UR value, section 3.4.4. |
| September 2023 | 17 | Revision of Table 4, section 3.5.<br>Modification of the last sentence, part 4. |