ANSES Opinion
Request No 2018-SA-0205
Related Request No 2011-SA-0354

The Director General

Maisons-Alfort, 22 January 2020

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

on the development of acute and chronic TRVs by the respiratory route for acrolein (CAS No. 107-02-8)

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 22 January 2020 shall prevail.

In 2018, ANSES issued an internal request to formulate toxicity reference values (TRVs) for acrolein, in connection with the internal request relating to the establishment of indoor air quality guidelines (IAQGs).

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 threshold 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.

As part of the work programme of ANSES's expert appraisal mission on indoor air quality guidelines (IAQGs), work on recommending short and long-term IAQGs for acrolein had been carried out in 2013. ANSES wished to capitalise on this work by proposing acute, subchronic and chronic TRVs by inhalation for acrolein.

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)".

ANSES entrusted examination of this request to the Expert Committee (CES) on "Health reference values". Two rapporteurs from this CES were appointed to monitor the work. The methodological and scientific aspects of the expert appraisal work were regularly submitted to the CES on "Health reference values". The report takes into account the comments and additional information provided by the members of this CES. The expert appraisal report and this opinion were validated by the CES on "Health reference values" on 28 November 2019.

This work was therefore conducted by a group of experts with complementary skills.

The summary of the toxicological data was based on summary reports by internationally recognised organisations (ATSDR, 2007; Ontario Ministry of the Environment, 2009; NRC, 2010; INRS, 1999; ANSES, 2014) supplemented by a literature search conducted from 2014 to September 2019.

3. ANALYSIS AND CONCLUSIONS OF THE CES

- **Summary of the toxicological data**

- Toxicokinetics

Acrolein is poorly absorbed following inhalation. Studies in dogs indicate that acrolein is retained in the upper respiratory tract (75-80%). Around 20% of the inhaled concentration reaches the lower respiratory tract. Acrolein reacts directly at the point of contact with the body following inhalation; this high reactivity therefore results in limited systemic distribution.

As with other highly reactive gases (Category 1), the local distribution of acrolein within the nasal cavity to the nasopharynx depends on the contact surface, the distribution of the inhaled airflow in the different zones encountered from the nose to the lung, and the airflow resistance in these different compartments.

There is limited information on the metabolism of acrolein. Metabolism takes place rapidly. The toxic potential of the conjugated metabolites is greatly reduced compared to acrolein. The main route of elimination is conjugation with glutathione (GSH) in tissues.

- Acute toxicity

Some early studies in humans have reported deaths following inhalation of acrolein (350 $mg.m^{-3}$ for 10 minutes).

Most of the available human data are derived from relatively old studies on healthy volunteers. Eye irritation is the most commonly described effect in humans following acute exposure to acrolein (from 0.14 $mg.m^{-3}$). Effects on the respiratory tract were also observed in these volunteers, such as irritation of the nose and throat after 5 seconds (2.8 $mg.m^{-3}$), nasal irritation after 10 minutes (0.35 $mg.m^{-3}$) and a significant decrease in respiratory rate after 35 minutes (1.4 $mg.m^{-3}$).

Numerous experimental studies in animals describe acrolein as a major respiratory toxicant: nasal irritation, difficulty breathing and damage to the respiratory tract and lungs have all been observed. Histological changes in the nasal cavity, respiratory epithelium, lungs, bronchi or trachea have also been found in rats, mice, hamsters, guinea pigs, dogs and rabbits (degeneration of the respiratory and olfactory epithelium and acute inflammatory reactions). Acrolein is regarded as a sensory irritant and is usually described by measuring the exposure concentration that leads to a 50% respiratory rate decrease (RD_{50}: 2.4 - 6.8 $mg.m^{-3}$ in mice and 11 - 21 $mg.m^{-3}$ in rats). Acrolein also causes mucus hypersecretion in rats, which is implicated in the development of chronic obstructive respiratory diseases. Bronchial hyperreactivity, which is characteristic of reactive airway diseases such as asthma, has been demonstrated in guinea pigs exposed to acrolein.

<u>Ocular effects</u>

Chronic exposure to acrolein vapours (4 - 8 $mg.m^{-3}$) causes eye irritation in dogs and monkeys, manifested by eye watering and closing of the eyelids. Rats and guinea pigs seem less sensitive.

Eye effects in humans following acute exposure are qualitatively similar to those observed in animal studies following acute exposure.

- Subchronic and chronic toxicity

<u>Respiratory effects</u>

Two epidemiological studies of indoor air pollution suggest an association between exposure to acrolein and the occurrence of respiratory effects (Annesi-Maesano *et al.*, 2011; DeCastro, 2014).

Various animal studies indicate that the respiratory system is the target organ of acrolein. The nasal mucosa is the most sensitive target. The severity of the respiratory effects increases with the acrolein concentration. Irritating and inflammatory effects on the respiratory system and histopathological changes have been observed in rats (from 0.9 $mg.m^{-3}$), hamsters (from 3.3 $mg.m^{-3}$), guinea pigs (from 1.6 $mg.m^{-3}$) and rabbits (from 1.6 $mg.m^{-3}$). The rat appears to be the most sensitive of all species, including humans, with effects appearing in the nasal cavity at the lowest doses.

- Genotoxicity

No studies have reported genotoxic effects of acrolein in humans or animals by any route of administration.

Acrolein is weakly mutagenic *in vitro* without metabolic activation in bacteria, and non-mutagenic with metabolic activation.

Concerning the *in vitro* genotoxic potential of acrolein, primary DNA damage (single-strand breaks and DNA and protein binding) has been observed in human fibroblasts and bronchial epithelial cells. **In conclusion, on the basis of *in vitro* studies, the CES considers that acrolein is weakly genotoxic in the current state of knowledge.**

- Carcinogenicity

No publications on carcinogenicity in humans were identified.

The International Agency for Research on Cancer (IARC) in 1995 and the United States Environmental Protection Agency (US EPA) in 2003 assessed the carcinogenic effects of acrolein and considered that there were insufficient data to be able to characterise its carcinogenic potential in humans (IARC Group 3). Acrolein is on IARC's 2020 work programme. Accordingly, this section may be updated in the light of any new findings.

In conclusion, the CES experts consider that acrolein is not carcinogenic in the current state of knowledge.

- Mechanisms of action

Acrolein is highly reactive, mainly with nucleophilic compounds, inducing protein and DNA modifications. In particular, it binds rapidly and irreversibly to molecules possessing a thiol group (-SH) such as glutathione, causing depletion of antioxidant defences, oxidative stress and impaired cell signalling. For example, in lung cells, acrolein can activate stress-dependent protein kinase pathways, induce the production of inflammation mediators and proteases, modify the innate immune response, induce mucus hypersecretion and cause epithelial damage. Co-exposure with glutathione or other compounds containing SH groups protects against the biological effects of acrolein, while conversely, glutathione depletion, caused by another xenobiotic for instance, increases acrolein's toxicity. Respiratory irritation from acrolein may be due to reactivity with the SH groups of the proteins making up the nasal epithelial cell receptors.

- Vulnerable population groups

Certain populations seem to be more susceptible to acrolein, in particular very young children, due to the immaturity of their airways, and people with certain disorders (eye, skin or respiratory disorders such as asthma) or allergies.

- **Development of acute, subchronic and chronic TRVs by inhalation**

1. Acute TRV by inhalation

Choice of the critical effect

Acrolein is an irritant of the airways and/or mucous membranes of the eye. The early symptoms observed following acute inhalation exposure are sensory irritation followed by damage to the airways (chemical burns). The nasal tissue appears to be the most sensitive target for sensory irritation, with a noticeable feeling of irritation occurring following exposure to 0.3 ppm for a few seconds. Higher concentrations (2-5 ppm) cause more severe irritation to the entire respiratory tract, followed by chemical burns.

The CES therefore decided to select sensory irritation of the upper respiratory system as the critical effect.

Analysis of the TRVs

Two acute TRVs by inhalation are available: one from the OEHHA (2008) of **2.5 µg.m^{-3}** (0.001 ppm) and one from the ATSDR (2007) of **6.9 µg.m^{-3}** (0.003 ppm).

The CES decided **not to select the OEHHA's TRV**. It considered the LOAEC from an experiment conducted with increasing concentrations of acrolein (Weber-Tschopp *et al.*, 1977) to be unreliable due to metrological difficulties (standard deviation of measurements unknown with concentration measurements obtained by colorimetry).

The ATSDR had selected the same key study as the OEHHA but instead considered the experiment conducted with a constant concentration, enabling it to be more confident of the concentration measured in the study by Weber-Tschopp *et al.* (1977). Several points were discussed by the CES members:

- The application of an uncertainty factor of 10 for the use of a LOAEC (UF_L) was not clearly explained in the ATSDR report, but the CES considered that a UF_L of 10 may be justified since effects occur at doses below the LOAEC used in the experiment by Weber-Tschopp *et al.* conducted at increasing concentrations (eye irritation from 0.09 ppm).
- The possible application of a time adjustment through application of a simplified Haber's law. According to this law, concentration and time are regarded as parameters with equivalent influence on toxicity. This leads to the view that the incidence and/or severity of an effect depends on total exposure to a potentially toxic substance without distinguishing between exposure peaks and exposure that is more spread out over time. However, it is commonly accepted that sensory irritant effects depend on the concentration rather than on the total dose and/or duration of exposure (Belkebir *et al.*, 2011). It would therefore be unnecessary to apply a time adjustment. Because its TRV was based on feelings of irritation in the nose and throat, the ATSDR correctly did not apply a time adjustment.

- Although more recent, the study by Dwivedi *et al.* (2015) does not call into question the study by Weber-Tschopp *et al.* (1977) used by the ATSDR to establish its value. Indeed, the study by Dwivedi *et al.* (2015) was carried out on a limited number of individuals (n = 18), showed no effect on respiratory function, and reported only a sensation of minor eye irritation at 0.1 ppm, which was not clinically confirmed.

The ANSES experts selected the ATSDR's TRV of 6.9 µg.m^{-3} (0.003 ppm), considering it to be of good quality. For irritating substances such as acrolein, the CES selects an application period of 24 h.

2. Subchronic TRV by inhalation

Choice of the critical effect

The critical effect selected following subchronic exposure to acrolein is damage to the respiratory epithelium of the upper airways. This damage is well documented with a causal relationship established on the basis of abundant animal and mechanistic data.

The ANSES experts consider the critical effect for subchronic exposure to be damage to the epithelium of the upper respiratory tract.

Analysis of the subchronic TRVs

Two subchronic TRVs by inhalation are available, proposed by the OEHHA (2008) and the ATSDR (2007).
The ATSDR had selected the study by Feron *et al.* (1978), which showed effects at the LOAEC in only one rat in 12. The CES experts consider that in view of the small number of rats affected and in the absence of any statistical study, this concentration cannot be regarded as a LOAEC, but gives an indication of the possibility of an effect at a concentration close to this value. The ATSDR's subchronic TRV based on the study by Feron *et al.* (1978) was therefore not selected due to the quality of this study.
Although based on a good quality study (Dorman *et al.*, 2008), the OEHHA's subchronic TRV cannot be used either. The OEHHA applied an allometric adjustment based on the use of a fluid dynamics model of the nasal cavity, and the establishment of this value therefore does not follow ANSES's methodological recommendations on establishing TRVs (ANSES, 2017).
The ANSES experts decided not to select the existing TRVs and proposed establishing a subchronic TRV.

Establishment of the subchronic TRV

- Choice of the key study and critical concentration

Two studies, Dorman *et al.* (2008) and Feron *et al.* (1978), had been selected by recognised international organisations for establishing a TRV.
Both studies exposed the entire bodies of the animals for 13 weeks and assessed many parameters including histopathological changes. They showed effects on the respiratory system, particularly in the nasal cavity, with a dose-response relationship. The analytical methods used by the authors were satisfactory and mean that neither of the studies is ruled out. Feron *et al.* (1978) injected the gas mixtures to which the animals were exposed directly into the chromatograph, coupled with a flame ionisation detector. Dorman *et al.* (2008) monitored the exposure concentrations by active sampling on 2,4-DNPH (after passing through an ozone filter to prevent interference), followed by extraction with acetonitrile and analysis by HPLC. Both studies can therefore be used for establishing a TRV.

The decision of the ANSES experts to choose the study by Dorman *et al.* (2008) rather than that of Feron *et al.* (1978) was based on various parameters:

In the study by Dorman *et al.* (2008), male Fisher rats (n = 360) were exposed for 13 weeks (6 hr/day, 5 d/week) via inhalation to concentrations of 0 - 0.02 - 0.06 - 0.2 - 0.6 and 1.8 ppm. The authors demonstrated dose- and location-dependent damage to the upper respiratory epithelium (hyperplasia, squamous metaplasia, inflammation) following exposure for at least 4 days to concentrations greater than 0.6 ppm. A NOAEC of 0.2 ppm was indicated by the authors.

- more animals per test (60 males/dose vs 6 animals/sex/dose),
- more doses tested (5 doses vs 3 doses),
- more sections of the nasal cavity examined (6 sections vs 3 sections),
- the incidence data was described, in contrast to the study by Feron *et al.*, 1978,
- the reliability of the critical dose: in the study by Feron *et al.* (1978), effects observed at the LOAEC occurred in only 1 of 12 rats. In view of the small number of rats affected and in the absence of any statistical study, this concentration cannot be regarded as a LOAEC but gives an indication of the possible effects at a concentration of this order of magnitude,
- the date of publication (2008 vs 1978).

However, Feron *et al.* (1978) exposed Wistar rats (n = 6/sex/group), Syrian hamsters (n = 10/sex/group) and Dutch rabbits (n = 2/sex/group) for 13 weeks (6 hours/day, 5 days/week) in inhalation chambers to 0 - 0.9 - 3.3 and 11.5 $mg.m^{-3}$ (0 - 0.4 - 1.4 and 4.9 ppm) (Feron *et al.*, 1978). Irritant and inflammatory effects on the respiratory system and histopathological changes were observed in rats, hamsters and rabbits, and indicate that the rat is the most sensitive species. The findings of this study, mainly those reported in rats, support the choice of the study by Dorman *et al.* (2008) as the source study.

The ANSES experts therefore selected the study by Dorman *et al.* (2008) as the key study.
The ANSES experts decided to adopt the NOAEC of 0.2 ppm (0.46 mg/m^3) proposed by Dorman *et al.* (2008) as the critical concentration.

- Time adjustment

In the study by Dorman *et al.* (2008), male Fisher rats (n = 360) were exposed for 13 weeks (6 hr/d, 5 d/week) via inhalation. Considering that acrolein is an irritant substance inducing tissue damage of the upper airways from repeated exposure, and in order to account for the discontinuity of exposure, a time adjustment was applied:

$NOAEC_{ADJ}$ = 0.2 x (6h/24h) x (5d/7d) = 0.2 x 0.18 = **0.036 ppm (0.08 $mg.m^{-3}$)**

- Allometric adjustment

A human equivalent NOAEC ($NOAEL_{HEC}$) was calculated from the NOAEC in the source study, to account for dosimetric differences between the animal species and humans. Acrolein is considered a Category 1 gas which, according to the US EPA, causes respiratory effects in the extra-thoracic region. In accordance with the TRV establishment method developed by ANSES, the experts applied the following formula:

$$NOAEC_{HEC} = NOAEC_{ADJ} \times \text{Regional Gas Dose Ratio} = NOAEC \times (V_A/SA_A)/(V_H/SA_H)$$

$$NOAEC_{HEC} = 0.036 \times [(0.2/15) / (20/200)] = \mathbf{0.0048\ ppm\ (0.01\ mg.m^{-3})}$$

Where: $NOAEC_{HEC}$ = NOAEC in humans

$NOAEC_{ADJ}$ = adjusted NOAEC in animals

V_A = ventilation rate in rats = 0.20 m^3/d

SA_A = surface area of the extra-thoracic region of rats = 15 cm^2

V_H = ventilation rate in humans = 20 m^3/d

SA_H = surface area of the extra-thoracic region of humans = 200 cm^2

- Choice of uncertainty factors

The TRV was calculated from the $NOAEC_{HEC}$ using the following uncertainty factors (ANSES, 2017):

- Inter-species variability (UF_A): **2.5**

An allometric adjustment was made to take interspecies variability into account, in order to be able to calculate a human equivalent concentration using the previously mentioned equation. To account for toxicodynamic variability and residual uncertainties, an additional uncertainty factor was set at 2.5 according to IPCS recommendations (IPCS, 2005) and based on ANSES's methodology (ANSES, 2017).

- Intra-species variability (UF_H)**: 10**

The factor 10 is chosen by default when using studies conducted in animals, to take into account the variability within the human species and vulnerable populations (mainly children, and related to asthma).

An overall uncertainty factor of 25 was therefore used for establishing the subchronic TRV.

- Proposed subchronic TRV and confidence level

$$TRV = NOAEC_{HEC} / UF = 0.01\ mg.m^{-3}/25 = \mathbf{0.44\ \mu g.m^{-3}\ (2.10^{-4}\ ppm)}$$

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

3. Chronic TRV by inhalation

Choice of the critical effect

The critical effect selected following chronic exposure to acrolein is damage to the respiratory epithelium of the upper airways. This damage is well documented with a causal relationship established on the basis of abundant animal and mechanistic data.
The ANSES experts consider the critical effect to be damage to the epithelium of the upper respiratory tract.

Analysis of the TRVs

Four chronic TRVs by inhalation are available, proposed by the OEHHA (2008), US EPA (2003), Health Canada (2000) and the WHO (2002).

The **Health Canada/WHO** TRVs were not selected because they are based on an acute study (Cassee *et al.*, 1996a).
The **US EPA's** chronic TRV based on the study by Feron *et al.* (1978) was not selected due to this study's low quality.
The **OEHHA's** chronic TRV, for which a time adjustment was applied, cannot be used, although it was based on a good quality study (Dorman *et al.*, 2008). The OEHHA applied an allometric adjustment based on the use of a fluid dynamics model of the nasal cavity, and the establishment of this value therefore does not follow ANSES's methodological recommendations on establishing TRVs (ANSES, 2017).

The ANSES experts decided not to select the existing TRVs and proposed establishing a chronic TRV.

Establishment of the chronic TRV

- Choice of the key study and critical concentration

Two studies, Dorman *et al.* (2008) and Feron *et al*. (1978), had also been selected by recognised international organisations for establishing a TRV.

The ANSES experts selected the study by Dorman *et al.* (2008) for the reasons presented in Section 2. The ANSES experts decided to adopt the NOAEC of 0.2 ppm (0.46 mg.m^{-3}) proposed by the authors as the critical concentration.

- Time adjustment

In the study by Dorman *et al.* (2008), male Fisher rats (n = 360) were exposed for 13 weeks (6 hr/d, 5 d/week) via inhalation. Considering that acrolein is an irritant substance inducing tissue damage of the upper airways from repeated exposure, and in order to account for the discontinuity of exposure, a time adjustment was applied:

$NOAEC_{ADJ}$ = 0.2 x (6h/24h) x (5d/7d) = 0.2 x 0.18 = **0.036 ppm (0.08 mg.m^{-3})**

- Allometric adjustment

A human equivalent NOAEC ($NOAEL_{HEC}$) was calculated from the NOAEC from the source study, to account for dosimetric differences between the animal species and humans. Acrolein is considered a Category 1 gas which, according to the US EPA, causes respiratory effects in the extra-thoracic region. In accordance with the TRV establishment method developed by ANSES, the experts applied the following formula:

$$NOAEC_{HEC} = NOAEC \times \text{Regional Gas Dose Ratio} = NOAEC \times (V_A/SA_A)/(V_H/SA_H)$$

$$NOAEC_{HEC} = 0.036 \times [(0.2/15) / (20/200)] = \mathbf{0.0048\ ppm\ (0.01\ mg.m^{-3})}$$

where: $NOAEC_{HEC}$ = NOAEC in humans

$NOAEC_{ADJ}$ = adjusted NOAEC in animals

V_A = ventilation rate in rats = 0.20 m^3/d

SA_A = surface area of the extra-thoracic region of rats = 15 cm^2

V_H = ventilation rate in humans = 20 m^3/d

SA_H = surface area of the extra-thoracic region of humans = 200 cm^2

- Choice of uncertainty factors

The TRV was calculated from the $NOAEC_{HEC}$ using the following uncertainty factors (ANSES, 2017):

- Inter-species variability (UF_A): **2.5**

An allometric adjustment was made to take interspecies variability into account, in order to be able to calculate a human equivalent concentration using the previously mentioned equation. To account for toxicodynamic variability and residual uncertainties, an additional uncertainty factor was set at 2.5 according to WHO-IPCS recommendations (WHO-IPCS, 2005) and based on ANSES's methodology (ANSES, 2017).

- Intra-species variability (UF_H): **10**

The factor 10 is chosen by default when using studies conducted in animals, to take into account the variability within the human species and vulnerable populations (mainly children, and related to asthma).

- Transposition from subchronic to chronic exposure (UF_S): **3**

An extrapolation from the subchronic effects was performed due to insufficient data on effects associated with chronic exposure. The duration of the selected key study, regarded in toxicology as "subchronic" (the animals were exposed for 5 days per week for 13 weeks), corresponds to approximately 10% of the life of the animals which, in humans, would correspond to about 7 years of exposure according to convention.

Similarly, the data are insufficient for determining whether similar effects could appear following chronic exposure to lower concentrations than those tested in the subchronic studies. In addition, other effects, not observed in subchronic exposure studies, could appear following repeated long-term exposure (chronic respiratory diseases).

Therefore, the ANSES experts decided to apply a value of 3 for this factor.

An overall uncertainty factor of 75 was therefore used for establishing the chronic TRV.

- Proposed chronic TRV and confidence level

$$TRV = NOAEC_{HEC} / UF = \mathbf{0.15\ \mu g.m^{-3}\ (6.10^{-5}\ ppm)}$$

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

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 formulation of acute, subchronic and chronic TRVs by inhalation for acrolein.

As a reminder, when dealing with TRVs and in line with the scenarios generally taken into account when assessing health risks in humans, ANSES distinguishes between three types of exposure duration:

- Acute exposure, from 1 to 14 days. For irritating substances such as acrolein, the CES selects an application period of 24 h;
- Subchronic exposure, from 15 to 364 days;
- Chronic exposure, for 365 or more days.

It should be noted that acrolein is on the IARC's 2020 work programme for a re-assessment of its carcinogenic potential. ANSES may be required to update the chronic TRV in the light of the IARC's findings.

An update of the long-term IAQG for acrolein may also be carried out in the light of the findings of this assessment.

Table 1: Acute, subchronic and chronic respiratory TRVs for acrolein

Type of TRV	Organisation (year)	Critical effect (key study)	Critical concentration	UF	TRV
Acute TRV	ATSDR (2007)	Nasal and throat irritation, decrease in respiratory rate Weber-Tschopp *et al.* (1977): study carried out in humans	LOAEC = 0.3 ppm	100 UF_H = 10 UF_L = 10	6.9 µg·m^{-3} (3.10^{-3} ppm) Confidence level High
Subchronic TRV	ANSES (2019)	Damage to the epithelium of the upper respiratory tract in adult Fisher rats Dorman *et al*. (2008)	LOAEC = 0.6 ppm NOAEC = 0.2 ppm Time adjustment $NOAEC_{ADJ}$ = 0.036 ppm (0.08 mg.m^{-3}) Allometric adjustment $NOAEC_{HEC}$ = 0.0048 ppm	25 UF_A = 2.5 UF_H = 10 UF_S = 1	0.44 µg.m^{-3} (2.10^{-4} ppm) Confidence level High
Chronic TRV	ANSES (2019)	Damage to the epithelium of the upper respiratory tract in adult Fisher rats Dorman *et al*. (2008)	LOAEC = 0.6 ppm NOAEC = 0.2 ppm Time adjustment $NOAEC_{ADJ}$ = 0.036 ppm (0.08 mg.m^{-3}) Allometric adjustment $NOAEC_{HEC}$ = 0.0048 ppm	75 UF_A = 2.5 UF_H = 10 UF_S = 3	0.15 µg.m^{-3} (6.10^{-5} ppm) Confidence level High

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KEYWORDS

Valeur toxicologique de référence, VTR, acroléine, inhalation, aiguë, subchronique, chronique.

Toxicity reference value, TRV, acrolein, inhalation, acute, subchronic, chronic.