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Cyanuric chloride

MAK Value Documentation – Translation of the German version from 2020

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Keywords

cyanuric chloride; irritation; respiratory tract; retrospective cohort study; sensitization; maximum workplace concentration; MAK value; hazardous substance

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated data for cyanuric chloride [108-77-0] considering all toxicological end points. Unpublished study reports and publications are described in detail. Cyanuric chloride is irritating to the nose, eyes and throat of workers (according to earlier studies at about 0.3 mg/m^3) and corrosive to the skin and eyes of rabbits and rats. The model best suited to estimate a long-term exposure threshold for workers with respect to lung function loss is based on a calculated cumulative exposure of 0.3 mg/m^3-years. An irritant effect was not reported. As wearing a protective mask was obligatory for workers exposed to higher cyanuric chloride concentrations, the extent to which the workers in this study were exposed is unclear. No NOAEC for repeated exposure of humans is known. A 90-day inhalation study with rats observed a small increase of inflammatory cells in the nose without other changes in the mucosa at 0.032 ml/m^3 (0.25 mg/m^3); the NOAEC is 0.0065 ml/m^3 (0.05 mg/m^3). A maximum concentration at the workplace (MAK value) of 0.001 ml/m^3 has been established based on the rat NOAEC after considering extrapolation to humans, a possible increase of effects with long-term exposure and the preferred value approach. Cyanuric chloride is classified in Peak Limitation Category I because of its local effects. As the human odour threshold is about 0.0025 ml/m^3, an excursion factor of 2 is set, although a NOAEC has not been established for sensory irritation in humans. A developmental toxicity study in rats determined a NOAEC of 50 mg cyanuric chloride/kg body weight and day, which corresponds to a concentration of about 11.5 ml/m^3 after toxicokinetic scaling; the margin to the MAK value is sufficiently large. Therefore, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and cyanuric chloride is assigned to Pregnancy Risk Group C. Cyanuric chloride is not mutagenic in vitro or clastogenic in vivo and no studies in germ cells are available. No carcinogenicity study was performed. Cyanuric chloride shows a skin sensitizing potential in animals and is therefore designated with "Sh" (for substances which cause sensitization of the skin). Data relating to a potential sensitization of the airways are not conclusive. The dermal absorption is expected to be low at non-irritating concentrations and does not contribute significantly to systemic toxicity.

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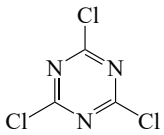
MAK value (2019)	**0.001 ml/m³ (ppm) ≙ 0.0076 mg/m³**
Peak limitation (2019)	**Category I, excursion factor 2**
Absorption through the skin	–
Sensitization (2019)	**Sh**
Carcinogenicity	–
Prenatal toxicity (2019)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
BAT value	–
Synonyms	cyanuryl chloride s-triazine trichloride trichlorocyanidine
Chemical name	2,4,6-trichloro-1,3,5-triazine
CAS number	108-77-0
Structural formula	
Molecular formula	$C_3Cl_3N_3$
Molar mass	184.4 g/mol
Melting point	147 °C (ECHA 2018)
Boiling point at 1013 hPa	192–195 °C (ECHA 2018; NLM 2018)
Vapour pressure at 20 °C	0.6 hPa (ECHA 2018)
log K_{OW}	2.14 at 25 °C (calculated; ECHA 2018) 0.512, temperature not specified (calculated; BUA 1994)
Solubility at 20 °C	poorly soluble in cold water, rapid hydrolysis to cyanuric acid and hydrochloric acid at 10 °C and above (Degussa 1988)
pH	1 after total hydrolysis (no other details; Degussa 1988)
1 ml/m³ (ppm) ≙ 7.652 mg/m³	**1 mg/m³ ≙ 0.131 ml/m³ (ppm)**

Among other sources, this documentation draws upon the dataset publicly available through REACH (ECHA 2018).

Cyanuric chloride is used in the production of herbicides for agriculture, textile dyes, optical brighteners, UV stabilizers for plastics and in the production of rubber products for the automotive industry (Morfeld et al. 2014). It is used also in the production of the precipitating agent sodium trithiocyanate, which is used for removing heavy metals from wastewater (BG RCI 1993).

Cyanuric chloride is a stable solid in dry air and undergoes hydrolysis upon contact with water, forming hydrochloric acid. It is produced at a purity of 99% (Morfeld et al. 2014).

Up to a concentration of 300 mg/m^3, smaller particles evaporate until the saturated vapour concentration is reached (BUA 1994; Degussa 1992).

1 Toxic Effects and Mode of Action

Cyanuric chloride is corrosive to the skin and eyes of rabbits and rats.

A report published in 1968 determined a one-minute irritation threshold of 0.3 mg/m^3 after the exposure of volunteers to cyanuric chloride vapour. However, the findings of this report can be used only as a guide. Earlier sources noted "acute effects" in workers in the form of irritation and corrosion of the skin and mucous membranes of the eyes and respiratory tract accompanied by severe coughing and bronchial obstruction, which later spread to the lower respiratory tract, pulmonary obstruction, bronchitis and bronchopneumonia. A long-term threshold value for cumulative exposure of about 0.3 mg/m^3 × years was calculated for workers in the cyanuric chloride production industry based on the estimated loss of lung function. No (acute) irritant effects were reported. However, it is questionable whether any noteworthy exposure occurred as the wearing of face masks was obligatory for most activities with potential exposure to cyanuric chloride.

Breathing difficulties were induced also in rats as a result of the local effects after single and repeated exposures. Whole-body exposure of rats to cyanuric chloride vapour at concentrations up to 0.25 mg/m^3 for 90 days induced slight effects in the respiratory tract. Oral exposure of rats led to irritation of the gastrointestinal tract, loss of body weight and mortality at doses of 4 mg/kg body weight and day and above.

No meaningful clinical findings in humans for the induction of sensitizing effects on the skin or airways by cyanuric chloride are available. The substance is sensitizing to the skin of mice and guinea pigs.

Cyanuric chloride yielded negative results in studies of genotoxicity in vitro and in vivo and in earlier carcinogenicity studies. The substance does not induce teratogenic effects.

2 Mechanism of Action

Cyanuric chloride undergoes hydrolysis upon contact with water, forming hydrochloric acid and cyanuric acid (Figure 1; Morfeld et al. 2014), which is in equilibrium with isocyanuric acid. The nucleophilic substitution of chloride may also occur. This reactivity with nucleophilic groups in proteins and other biomolecules may be responsible for the sensitizing and irritant effects.

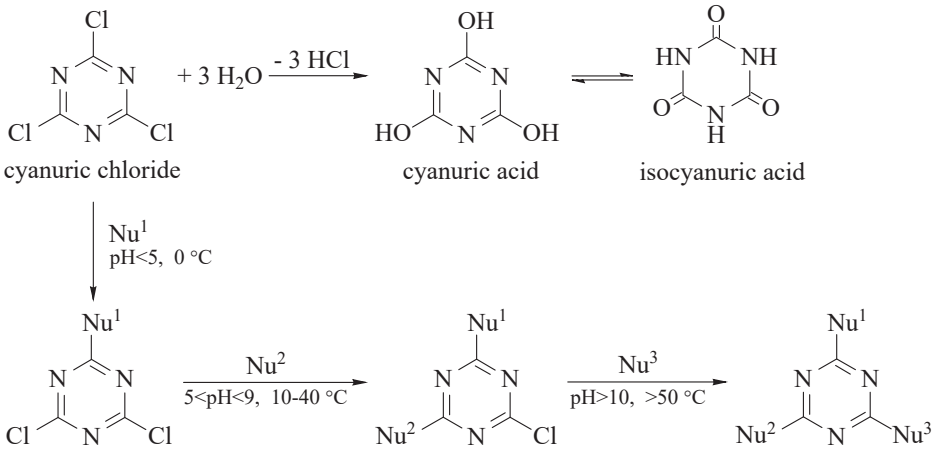


Fig. 1 Reaction pathways of cyanuric chloride; Nu: nucleophile

3 Toxicokinetics and Metabolism

After inhalation, oral or dermal exposure, cyanuric chloride breaks down to cyanuric acid and hydrochloric acid upon contact with water. The hydrolysis product of cyanuric chloride, cyanuric acid, is almost completely absorbed in humans after oral administration (ECHA 2018).

It is unlikely that cyanuric chloride breaks down to cyanide in vivo, as the thiocyanate levels in serum remained unchanged in rats after repeated exposure (BUA 1994).

4 Effects in Humans

4.1 Single exposures

In a poorly documented report published in Russian in 1968, a one-minute irritation threshold of 0.3 mg/m^3 was established after the exposure of volunteers to cyanuric chloride vapour. No symptoms were observed at the concentration of 0.13 mg/m^3 (Blagodatin 1968). As the methods and results were not sufficiently documented, the findings can at best be considered an indication of a possible irritation threshold.

The acute effects observed in humans were coughing caused by bronchial obstruction in addition to bronchitis and bronchopneumonia (no other details; BG RCI 1993; BUA 1994).

A study evaluated the occupational health data relating to short-term, accidental exposure to cyanuric chloride provided by the medical service of the Münchsmünster plant of SKW Trostberg AG for a collective of 39 employees who had worked in cyanuric chloride production for an average 9.7 years (concentration not specified). Effects on the eyes were the primary effects. Exposure to cyanuric chloride dust caused irritation of the conjunctiva of the eyes, coughing, breathing difficulties and dyspnoea. The symptoms subsided after a short period of time. No cases of chronic complaints or permanent damage are known (Mertschenk et al. 1998).

The odour thresholds for cyanuric chloride were determined in 12 test persons by olfactometer using a standard test method. The threshold values ranged from 0.007 to 0.069 mg/m^3. After excluding the data for 2 test persons who were extremely hyposensitive and 2 whose odour detection thresholds for the standard reference material *n*-butyl alcohol were not in the required range, the mean odour threshold value for cyanuric chloride was 0.019 mg/m^3. The odour of the substance was described as pungent (Mannebeck et al. 1999). When all test persons were included in the evaluation, the mean odour threshold was 0.024 mg/m^3. Overall, the odour threshold is assumed to be about 0.02 mg/m^3.

4.2 Repeated exposure

In addition to local irritation, central nervous system disorders, insomnia, headaches and physical weakness were observed in workers exposed to cyanuric chloride vapour. However, the study report did not include data for the exposure concentrations. The data for the effects on the cardiovascular system are inconsistent (BG RCI 1993; BUA 1994). The studies carried out in the Soviet Union in the 1980s reported effects that were not found in studies carried out at workplaces in Germany over a period of 20 years (BUA 1994).

After repeated exposure, the effects observed were irritation and corrosion of the skin and the mucous membranes of the eyes, conjunctivitis with lacrimation, and irritation and corrosion of the respiratory tract with increased production of mucous in the nose. Cyanuric chloride gas and dust induced severe coughing and bronchial obstruction which later spread also to the lower respiratory tract after a delay. Pulmonary obstruction, bronchitis and bronchopneumonia were observed in addition to an increased incidence of asthma (BUA 1994). The data are not sufficient to establish a concentration–effect relationship.

A study evaluated the occupational health data provided by the medical service of the Münchsmünster plant of SKW Trostberg AG for a collective of 39 employees who had worked in cyanuric chloride production for an aver-

age 9.7 (1–22) years. According to the authors, the highest levels of exposure occurred during "big bag filling" with mean concentration levels (not specified whether arithmetic or geometric) of 92.8 ± 147.5 µg/m^3. The exposure levels of the workers of the filling station were determined by personal air monitoring and were equivalent to the 8-hour time-weighted average. Levels of 7.1 ± 9.2 and 4.4 ± 2.7 µg/m^3, respectively, were recorded by stationary determination at the filling station and in the area surrounding the exhaust system during "big bag filling". Irritant effects were not reported and lung function tests (forced expiratory volume in one second (FEV_1)) carried out with the 39 workers yielded results that were on average 97% of the reference value (Mertschenk et al. 1998).

A longitudinal epidemiological study (retrospective cohort study) was carried out with 427 male workers employed by Evonik Industries AG at 3 production sites for cyanuric chloride. The employees had worked at the sites for at least 12 months between 1958 and 2007. As no acute irritant effects were observed in the workers, the study investigated the long-term effects of cyanuric chloride exposure on the respiratory system. Thirty-three persons were excluded from the study because of a lack of medical files (n = 14), a lack of exposure to cyanuric chloride (n = 5) and an insufficient length of employment (n = 14). The final study collective was made up of a total of 394 persons who had worked at the plants for longer than 12 months; the majority (n = 310) were entry-level workers. The study design (entry-level cohort) makes the "healthy worker hire effect" unlikely. The mean age of the workers was 47.5 years at the time of the last medical examination. The start of cyanuric chloride production at the respective sites Antwerp, Münchsmünster or Wesseling was chosen as the starting point of the study. At all production sites, the level of exposure was always dependent upon the activities being carried out, the place, the time and whether the activity was being performed in a mandatory mask zone. Exposure levels were determined by personal air monitoring and stationary determinations or based on expert knowledge of the respective workplace. Exact exposure data for individual days are not available. A total of 188 determinations were taken at the three plants during the study period. Of these, 64 were not included in the evaluation as the workers wore face masks. Fifty-seven of the determined values were below the detection limit of 0.003 mg/m^3 for the procedure and 67 values were above. The exposure levels for all 394 exposed persons were estimated from these 67 values. Expert estimates were used to extrapolate individual levels of exposure to cyanuric chloride in the past from the small number of what were, essentially, more recent values. The calculated exposure concentrations showed that concentration levels had declined since the 1970s. Rather than the threshold value of 0.019 mg/m^3 reported by Mannebeck et al. (1999), this study used an odour threshold of 0.0385 mg/m^3 calculated by taking the mean of the minimum and maximum values of 0.007 and 0.07 mg/m^3, respectively. An empirical value derived from internal data obtained at the production sites of Evonik Industries AG was used to determine the threshold value in mandatory mask zones; this value was twice the odour threshold value and thus equalled a mean value of 0.077 mg/m^3 (min. = 0.014, max. = 0.14 mg/m^3). The concentration levels determined behind the filters of the masks were below the detection limit for the procedure. To determine the level of exposure of workers wearing masks, the exposure concentration was assumed as the detection limit. The worker's work biography, smoking habits, basic biometric data and lung function parameters were evaluated in addition to co-exposures and past exposure through earlier activities, and the findings were condensed into annual datasets. Cross-sectional data were collected also for chronic bronchitis, dyspnoea, asthma, chronic-obstructive pulmonary disease (COPD) and sensitization parameters. The collective was made up of 160 active smokers, 78 former smokers and 149 men who had never smoked. The cumulative amount of smoke (cumulative exposure to cigarettes) was included in the evaluation of the lung function parameters. On the basis of the results of the last examination of the 385 study participants and taking data for smoking habits into account, the prevalence of stage II or higher COPD was calculated to be 6.8%. This included data for 148 persons who had never smoked; the prevalence of stage II or higher COPD in this group was 0.7%. Studies that investigated the worldwide prevalence of COPD in the general population (Buist et al. 2007) determined a prevalence of (stage II or higher) COPD in men of 11.8%. When compared with this value, the examined study population did not have an increased prevalence of COPD. For all workers, the mean total cumulative exposure to cyanuric chloride was 0.217 mg/m^3 × years (min. = 0.005, max. = 0.941 mg/m^3 × years). The mean cyanuric chloride concentration per exposure year was 0.020 mg/m^3 (min. = 0.003, max. = 0.051 mg/m^3). The workers were exposed also to hydrochloric acid, calcium chloride, sodium dicyanamide (dust), acetone cyanohydrin, hydrogen cyanide, cyanamide, cyanogen chloride, methanol and methyl chloride. Hydrogen cyanide, acetone cyanohydrin and sodium dicyanamide did not have any effect on lung function parameters and are thus not regarded as confounders. Unlike these, calcium chloride and hydrochloric acid

did have an effect on lung function parameters and are thus potential confounders. Overall, the results of 2983 lung function tests are available for the parameters VC (vital capacity), FVC (forced vital capacity) and FEV_1. When compared with the external reference values, the mean values determined for the lung function parameters were in the normal range. Overall, the test persons were from four occupational groups (production workers, delivery workers, packing and shipping workers, laboratory workers). A subgroup analysis was carried out for the occupational group of production workers (288 persons): the estimated risk for the effects on lung function parameters following exposure to cyanuric chloride was in the range of that estimated for the entire cohort (VC_{max} (maximum vital capacity): −0.443 l/(mg/m^3 × years), $p = 0.154$; FEV_1: −1.017 l/(mg/m^3 × years), $p < 0.001$). The analysis of the values determined for specific IgE found evidence of sensitization to cyanuric chloride without any effects on lung function values. There was a higher incidence of a number of respiratory symptoms such as asthma (33), chronic bronchitis (14, none of them non-smokers) and stage I a (38) and II a (18) COPD (Evonik Technology & Infrastructure GmbH 2018; Morfeld et al. 2014). The results for these symptoms were presented in a separate publication (Morfeld and Noll 2014).

An important part of the evaluation of the findings of the cohort study was a longitudinal analysis of exposure and medical response variables. As continuous target variables, the lung function parameters FEV_1, FEV_1% and VC_{max} were examined both longitudinally and in cross-section. In the longitudinal analysis, lung function disorders were evaluated as categorized variables, which were defined as stage I a and II a COPD according to the GOLD standard (Global Initiative for Chronic Obstructive Lung Disease). Mild COPD was determined in 56 of the 391 study participants (14.3%). The prevalence of COPD (stage II severity and higher) in study participants with cumulative exposure to cyanuric chloride below the estimated threshold of 0.3 mg/m^3 × years was 6.5%. This is slightly lower than the prevalence determined in persons with high levels of exposure (6.9%). The cross-sectional analysis considered additional categorized variables for the evaluation of lung function disorders such as asthma, dyspnoea and chronic bronchitis. For the whole cohort, the individual model analyses yielded some indications of lung-function impairment following long-term exposure to cyanuric chloride. The multi-model analysis did not provide conclusive evidence of effects induced by exposure to cyanuric chloride, but it did indicate a possible adverse effect on the lung function parameters VC_{max} and FEV_1. In the longitudinal analysis, the risk estimates for cyanuric chloride exposure for the subgroup of non-smokers determined using generalized estimating equation regression models were comparable with those for the whole cohort. When models with maximum estimates of pulmonary function loss were considered, a long-term threshold value for cumulative exposure of about 0.2 mg/m^3 × years was identified. When a more representative model that described the estimated average loss was used, the result was a threshold range from 0.2 to 0.4 mg/m^3 × years (Evonik Technology & Infrastructure GmbH 2018; Morfeld and Noll 2014).

The authors of the publication suggested that the additional lung function loss induced by exposure to cyanuric chloride (which is about 5% to 10% higher than the normal amount of loss) was "tolerable" (Morfeld and Noll 2014). The Commission categorically rejects this viewpoint and asserts that any additional loss in lung function induced by a chemical substance is not to be regarded as tolerable.

The data were re-evaluated by performing a subgroup analysis of the estimated threshold values. The data were broken down into three exposure categories: < 0.1 mg/m^3 × years, 0.1 to 0.3 mg/m^3 × years and > 0.3 mg/m^3 × years. No changes to the FEV_1 values of the workers were observed in the lower two groups up to the end of the follow-up period (Evonik Technology & Infrastructure GmbH 2018).

Summary: Overall, the study findings are difficult to interpret. Actual exposure concentrations are available only in a few cases. The wearing of face masks was required during most of the activities with potential exposure to cyanuric chloride. The greatest effects on lung function parameters were noted in the group of smokers (including former smokers). The findings in the workers of the different plants were of varying severity and it is unclear whether the evaluation of cumulative exposure is a suitable parameter for a substance causing acute irritation. As irritation was not observed in the workers at any point of the study, it is questionable whether they were exposed to cyanuric chloride to a relevant degree.

4.3 Local effects on skin and mucous membranes

Acute and repeated exposure to the substance caused irritant and corrosive effects on the skin and mucous membranes of the eyes, such as conjunctivitis with lacrimation, and of the respiratory tract, such as increased production of mucous in the nose. Cyanuric chloride gas and dust caused severe coughing and bronchial obstruction, which later spread to the lower respiratory tract after a delay. Pulmonary obstruction, bronchitis and bronchopneumonia were observed (BUA 1994).

4.4 Allergenic effects

4.4.1 Sensitizing effects on the skin

An earlier publication reported eczematous, in some cases blistery, skin reactions in four workers who handled cyanuric chloride or substances made from cyanuric chloride over a longer period of time. Two of the cases involved a female laboratory worker and another employee who were repeatedly exposed to cyanuric chloride or to cyanuric chloride and an optical brightener made with the substance in the course of their work. The other two employees were probably exposed (only) to dyes synthesized using cyanuric chloride. Patch tests with 25% to 50% formulations of the products in the 3 workers who were exposed to these products and patch tests with cyanuric chloride in all four tested persons yielded positive results. The report did not specify which cyanuric chloride concentrations were used. It is likely that the tests were carried out with the undiluted substance; this makes the findings unsuitable for the evaluation of the sensitizing effects of the substance (Sonneck 1961).

4.4.2 Sensitizing effects on the airways

An increased incidence of asthma was found in a plant in which cyanuric chloride was processed (BG RCI 1993).

A number of reviews list cyanuric chloride as a substance that causes sensitization of the airways (Basketter et al. 2017; Kirchner 2002); however, there are no well-documented case studies of the induction of allergic respiratory diseases by cyanuric chloride.

An engineer who was only occasionally, but never directly, exposed to cyanuric chloride over a period of 6 months as he went on rounds in a production plant in which cyanuric chloride was used for synthesis, reported a chronic cough that persisted after an infection with fever. Auscultation and lung function tests did not determine unusual findings and a radioallergosorbent test (RAST) for the detection of specific IgE against cyanuric chloride–human serum albumin (HSA) conjugates yielded positive results (no other data) (Alt and Diller 1988).

Coughing or occupational dyspnoea and symptoms in the upper respiratory tract and conjunctivae or both groups of symptoms were each determined in about a third of 21 workers with exposure to cyanuric chloride who were suspected of having developed occupational asthma after 1 month to 29 years (on average 5 years). In 2 workers, asthma symptoms developed after accidental exposure to high concentrations of cyanuric chloride. Specific IgE was determined in 80% of the workers (no other details) and an occupational disease was diagnosed in 6 cases. Specific IgE was determined in 3 of the 466 exposed, asymptomatic workers, while specific IgE was not found in 55 persons without exposure (ECHA 2018).

In a collective of 19 workers involved in cyanuric chloride production, total IgE and specific IgE against cyanuric chloride–HSA conjugates were determined. The total IgE levels were between 44 and 850 IU/ml. In the control group of 14 workers who were not exposed to cyanuric chloride, the total IgE levels were between 2 and 820 IU/ml. In the control group, the binding percentage of specific IgE determined by RAST assay was between about 1% and about 7.5%. In 5 persons from the exposure group, the percentage of specific IgE determined by RAST analysis ranged from 9.3% to 60.7% and RAST inhibition tests yielded values of at least 25%. Taken together, these findings were regarded as evidence of sensitization. However, the report did not specify whether these persons had previously experienced respiratory symptoms (Karol et al. 1995). In a later study, specific IgE against cyanuric chloride–HSA conjugates were

determined in the sera of 10 workers exposed to cyanuric chloride. RAST inhibition tests were performed in 3 cases, each of which found inhibition levels above 70% (Jones et al. 1998). The report did not include data for clinical symptoms in the workers and it is not clear whether these were a subcollective of the previous study.

In a study collective consisting of 394 men exposed to cyanuric chloride in 3 plants producing the substance, the mean total cumulative exposure was 0.217 mg/m^3 × years (minimum: 0.005, maximum: 0.941 mg/m^3 × years) and the mean cyanuric chloride concentration per exposure year was 0.020 mg/m^3 (minimum: 0.003, maximum: 0.051 mg/m^3). A total of 2983 tests carried out to evaluate the lung function parameters VC, FVC and FEV_1 did not demonstrate an increased incidence of lung disorders. When the final determinations were made, the values for VC and FVC were on average 103% and the values for FEV_1 were on average 99% of the reference values. Patient histories from 157 persons were obtained by survey (5 × dyspnoea, 33 × asthma, 14 × chronic bronchitis, 38/26 × stage I a/II a COPD). Sensitization to cyanuric chloride was determined in 130 persons by fluorescent enzyme immunoassay (FEIA) on the basis of specific IgE against cyanuric chloride–HSA conjugates. Twenty-two of the values were above the detection limit of 0.1 kU/l; 15 of these were higher than 0.35 kU/l. Ten of the 15 values that were above the reference value were determined in 70 persons from one of the three plants; in total, 120 of the workers included in the study worked at this plant. Unlike at the other two plants, the production line at this plant was an "open" system and face masks had (no longer) been mandatory for 15 years. At this plant, the mean level of specific IgE was 1.88 kU/l; the levels determined at the other two plants were 0.4 kU/l and 0.19 kU/l. Confirmed cases of sensitization could not be correlated with either lung function impairment or symptoms of illness (Morfeld et al. 2014; Morfeld and Noll 2014).

The occupational health data provided by the plant medical service for a collective of 39 workers who had worked in cyanuric chloride production for an average 9.7 years were evaluated. The levels of exposure were 7.1 ± 9.2 µg/m^3 (stationary determinations during "big bag filling"), 4.4 ± 2.7 µg/m^3 (stationary determinations in the vicinity of the exhaust system) and 92.8 ± 147.5 µg/m^3 (personal air monitoring) (Mertschenk et al. 1998). The study did not find evidence of a sensitization potential.

4.5 Reproductive and developmental toxicity

There are no data available.

4.6 Genotoxicity

There are no data available.

4.7 Carcinogenicity

There are no data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

A number of earlier studies (1976–1992) were carried out with cyanuric chloride in the form of a vapour or an aerosol/vapour mixture to determine the LC_{50} in rats. A 4-hour LC_{50} of between 25 and 180 mg/m^3 was determined for the vapour and a 4-hour LC_{50} of between 43 and 170 mg/m^3 was determined for the aerosol/vapour mixture. At the time of determination, 25% to 100% of the dust particles were smaller than 3 µm. Both exposure to the vapour and to the aerosol/vapour mixture induced similar symptoms to a similar degree of severity. In mice, a 2-hour LC_{50} of 10 mg/m^3

was determined for the vapour. The symptoms observed were irritation of the eyes and the respiratory tract including abnormal breathing sounds, watery eyes, laboured breathing and even central nervous system effects such as apathy, ataxia, tremor, slower reflexes and general weakness in addition to losses in body weight and cyanosis. At higher concentrations, mortality was observed during the exposure period. At lower concentrations, mortality caused by obstructive changes in the respiratory tract occurred up to 4 weeks after exposure. The lungs were found to have partially collapsed; they were oedematous with discoloration or liverlike in appearance. The bronchi contained foam or viscous mucous. Also the mucous membranes in the gastrointestinal tract were reddened and dilated by the formation of gas and the kidneys and liver were pale (BUA 1994).

In a study carried out according to OECD Test Guideline 403, groups of 5 male and 5 female Wistar rats were exposed to cyanuric chloride concentrations of 0, 37.6, 150.6, 177.3, 289.3 or 449 mg/m^3 for 4 hours and observed for a period of 4 weeks. The 4-hour LC_{50} was 170 mg/m^3. Exposure to the undiluted cyanuric chloride aerosol took place nose-only. At concentrations of 37.6 mg/m^3 and above, concentration-dependent irritation of the respiratory tract, laboured and slowed breathing, serous nasal discharge, reduced motility and unkempt fur were observed. These effects subsided after 5 days. At concentrations of 150.6 mg/m^3 and above, also dyspnoea, atony, bloody and a blood-encrusted rhinarium (mucous membrane around the nostrils), cyanosis, cachexia, and reduced grip strength and responsiveness were reported. Mortality occurred between days 4 and 28. These effects intensified with the increase in concentration (Degussa 1992). Up to a concentration of 300 mg/m^3, smaller particles evaporated until the vapour concentration was saturated (BUA 1994; Degussa 1992). The combined LC_{50} for the male and female rats was 170 mg/m^3; 150 mg/m^3 for the males and 201 mg/m^3 for the females (ECHA 2018).

5.1.2 Oral administration

In a study carried out according to OECD Test Guideline 401, 10% cyanuric chloride in polyethylene glycol was given to groups of 5 male and 5 female Wistar rats in gavage doses of 100 to 750 mg/kg body weight. The LD_{50} in male rats was 315 mg/kg body weight, in female rats 356 mg/kg body weight. Accelerated breathing, unkempt fur and drowsiness were observed; death was preceded by hypokinesis, reduced muscle tone, loss of the righting, pain and pupillary light reflexes, piloerection and reduced body temperature. No clinical signs of toxicity were induced at a dose of 240 mg/kg body weight; at higher doses, signs of toxicity were noted about 30 minutes to 3 hours after administration of the substance. The walls and mucosa of the stomach and intestines were reddened and thickened. Bleeding, cellular infiltration and mucosal ulceration were found in the glandular stomach (Nofer Institute of Occupational Medicine 1993 a).

Other studies determined the following LD_{50} values: 300 to 1170 mg/kg body weight in rats, 350 to 1000 mg/kg body weight in mice, 340 to 380 mg/kg body weight in rabbits and 500 to 1000 mg/kg body weight in dogs. However, these studies were considered unreliable in the REACH registration dossier (ECHA 2018).

The oral LD_{50} in rats was between 166 and 1170 mg/kg body weight (BG RCI 1993; BUA 1994). Studies that used polyethylene glycol as the vehicle reported lower values than those that used arachis oil as the vehicle (BUA 1994).

5.1.3 Dermal application

In a study carried out according to OECD Test Guideline 402, occlusive application of a single cyanuric chloride dose of 2000 mg/kg body weight (white solid in kerosine) on the dorsal skin of 3 male and 3 female rabbits (White Russian) did not lead to death or signs of systemic effects. When the patch was removed, the skin area was found to be reddish-brown in colour, swollen and hardened. Acanthosis and hyperkeratosis in addition to subchronic inflammatory changes with ulceration and epidermal necrosis were determined by histopathological examination of the skin (Degussa 1988).

Another study with Tif: RAIf rats reported dyspnoea, exophthalmos, ruffled fur and a general deterioration of the reflexes, but no mortality. In all animals, oedema, erythema and necrosis were observed at the application site (BUA 1994).

The dermal LD_{50} in rats (BG RCI 1993) and rabbits (BUA 1994) was above 3000 mg/kg body weight. Mortality did not occur up to this dose.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In earlier studies that were not described in great detail, irritation was observed after exposure of rats to a concentration of 1.8 mg/m³ for 2.5 months and "no toxicity" was observed after exposure to 0.3 mg/m³ for 5 months (BUA 1994).

The report for the 90-day study described below includes a 28-day range-finding study which observed a slight decrease in body weights, reduced erythrocyte counts, lung congestion and focal necrosis in the mucosa of the nose, trachea and bronchi in addition to proliferation of the bronchus-associated lymphatic tissue of the rats at a concentration of 0.4 mg/m³. The NOAEC (no observed adverse effect concentration) was 0.08 mg/m³ (Table 1; Nofer Institute of Occupational Medicine 1994 c). As a detailed report is not available for the range-finding study, its findings can be used only as a guide, assuming that the study protocol and analysis were carried out using a procedure similar to that of the 90-day study.

In a 90-day inhalation study with Wistar rats (not specific pathogen free (SPF) animals), exposure to the highest cyanuric chloride concentration tested of 0.25 mg/m³ did not lead to clear substance-induced findings. No systemic effects were observed. The incidences of the local effects are shown in Table 1. In the high concentration group, yellow exudate in the nose was observed in 6/10 male rats. This effect was not observed in the male control animals and occurred with the same incidence in the females of all concentration groups (2/10). Lung congestion was observed in 3/10 males and 2/10 females of the high concentration group, but not in the control animals. Polymorphonuclear lymphocytes in the nasal lumen were observed in 6/10 male animals of the high concentration group. The incidence of foamy macrophages and infiltration of lymphocytes in the alveolar septa was increased. No effects occurred with an increased incidence in the lower concentration groups. However, after re-evaluating the histopathological sections, "some of which could no longer be found, some of which had faded, but in general could still be used for evaluation", the authors concluded that the effects were probably not induced by the substance, but were more likely the result of an infection that occurred in all groups (Nofer Institute of Occupational Medicine 1994 c, 1997). The study was not well documented; irregularities were found during the re-evaluation and not all findings were included in the evaluation. The re-evaluation was carried out by the husband of the pathologist who had originally performed the study and by a representative of the study's sponsors. A (mild) infection is plausible because the nasal mucosa was infiltrated with lymphocytes and the increase in cells in the bronchus-associated lymphatic tissue was found also in the control animals. A marked independent effect appears to have not been induced, at least in this concentration range, as the effects determined in the exposed groups were similar to those found in the control animals, at least in one sex. However, the question whether an infection may have concealed mild effects induced by the substance cannot be resolved with certainty.

Summary: On the basis of the report for the 90-day inhalation study in rats, it is not possible to determine whether the findings in the nose observed at a concentration level of 0.032 ml/m³ (0.25 mg/m³) were caused by an infection or were a substance-induced effect. However, as these effects occurred mainly after exposure to the high concentration, the Commission has derived a LOAEC (lowest observed adverse effect concentration) for cyanuric chloride of 0.032 ml/m³ (0.25 mg/m³) and a NOAEC of 0.0065 ml/m³ (0.05 mg/m³). In view of the findings in the respiratory tract of rats reported by the 28-day range-finding study, which are available only in abridged form, and the fact that the substance is an irritant, it is plausible that the first signs of an irritant effect induced by cyanuric chloride would occur after exposure to a concentration of 0.032 ml/m³ (0.25 mg/m³).

Tab. 1 Effects induced by cyanuric chloride after repeated inhalation exposure

Species, strain, number per group	Exposure	Findings	References
rat, no data	**28 days**, 0, 0.08, 0.4 mg/m³, vapour, whole-body, 6 hours/day, 5 days/week	**included in the report of the 90-day study as a range-finding study – no other data:** **0.08 mg/m³**: **NOAEC**; **0.4 mg/m³**: slight decrease in body weights, slight decrease in number of red blood cells, congestion in the lungs, focal necrosis in the mucosa of the nose, trachea and bronchi, BALT proliferation	ECHA 2018; Nofer Institute of Occupational Medicine 1994 c
rat, Wistar, 10 ♂, 10 ♀	**90 days**, 0, 0.01, 0.05, 0.25 mg/m³, vapour, whole-body, 6 hours/day, 5 days/week; purity > 95%	**control and exposed animals**: infiltration of lymphocytes in the nasal mucosa (♂: 6/10, 2/10, 8/10, 4/10; ♀: 5/10, 4/10, 8/10, 7/10), number of cells in the BALT ↑ (♂: 3/10, 4/10, 2/10, 7/10; ♀: 6/10, 2/10, 3/10, 4/10); **0.05 mg/m³**: **NOAEC**; **0.25 mg/m³**: LOAEC, mild local irritation – unclear whether induced by the substance or by a (mild) infection: number of animals with yellow exudate in the nose ↑ (♂: 0/10, 1/10, 1/10, 6/10; ♀: 2/10, 2/10, 2/10, 2/10), polymorphonuclear lymphocytes in the nasal lumen ↑ without changes in the mucosa (♂: 0/10, 1/10, 1/10, 6/10; ♀: 2/10, 2/10, 2/10, 2/10), lung congestion (♂: 0/10, 0/10, 0/10, 3/10; ♀: 0/10, 0/10, 0/10, 2/10), slight increase in the infiltration of lymphocytes in the alveolar septa (♂: 1/10, 5/10, 3/10, 7/10; ♀: 2/10, 2/10, 4/10, 3/10), slight increase in the number of foamy macrophages (♂: 1/10, 2/10, 0/10, 5/10; ♀: 1/10, 0/10, 3/10, 2/10)	ECHA 2018; Nofer Institute of Occupational Medicine 1994 c, 1997
rat, no data, 10	**2.5 months**, 0, 1.88 mg/m³, not specified whether only vapour or an aerosol/vapour mixture, 4 hours/day, 5 days/week	**incomplete description of the study method and results**; **1.88 mg/m³**: irritation of the mucosa of the eyes and respiratory tract, animals lethargic, body weight gains ↓, from week 6 onwards: mortality 3/10 (bronchopneumonia), body temperature ↓ by 1 °C, oxygen consumption ↓, number of red blood cells ↓, Hb level ↓, nodular interstitial pneumonia, weak granular dystrophy in liver, kidneys and myocardium	BUA 1994
	5 months, 0, 0.3 mg/m³, not specified whether only vapour or an aerosol/vapour mixture, 4 hours/day, 5 days/week	**incomplete description of the study method and results**; **0.3 mg/m³**: "non-toxic, NOAEL"	

BALT: bronchus-associated lymphoid tissue; Hb: haemoglobin

5.2.2 Oral administration

In rats given subacute oral doses of cyanuric chloride, local irritation in the gastrointestinal tract, loss of body weight and mortality were observed. "Pathological findings" were determined in the liver, spleen and lungs (BUA 1994). However, none of the original publications are available. These included a study in rabbits from 1952, a 30-day study in rats available only in the form of a personal communication from 1979, a dose-finding study from 1983 that did not provide any information about the laboratory or sponsor and the summary of a study carried out by the Nofer Institute of Occupational Medicine, which was published in 1990 only in the form of an abstract. The study report itself appears to no longer exist. The insufficient documentation precludes the use of these studies for the evaluation of the toxicity of the substance after oral exposure (Table 2).

Tab. 2 Effects induced by cyanuric chloride after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, CD, 5 ♂, 5 ♀	**5 days**, gavage, in mineral oil, 0, 10, 20, 40, 80, 160, 320 mg/kg body weight and day, 5 days/week	**dose-finding study**; **10 mg/kg body weight**: "NOAEL"; **20 mg/kg body weight and above**: breathing difficulties, salivation, motor activity ↓, dose-dependent reduction in feed consumption and body weight gains, dose-dependent: dark discoloration, haemorrhaging, erosion and ulceration in the stomach; **40 mg/kg body weight and above**: mortality; **320 mg/kg body weight**: mortality 10/10 within 4 days	BUA 1994; ECHA 2018
rat, Wistar, 8 ♂, 8 ♀	**28 days**, gavage, vehicle not specified, 0, 4, 20, 100 mg/kg body weight and day, 7 days/week	**abstract**, similar to OECD Test Guideline 407; effects induced by irritation, immunological effects possible; **4 mg/kg body weight**: mortality ♀ (1/8), dose-dependent histopathological findings corresponding to the irritant effects in the gastrointestinal tract, liver, spleen and lungs; **20 mg/kg body weight**: mortality ♂ (1/8) and ♀ (2/8); **100 mg/kg body weight**: mortality ♂ (6/8) and ♀ (3/8), feed consumption ↓, body weights ↓, red blood cells ↓, haemoglobin levels ↓, haematocrit ↓, alkaline phosphatase ↑, relative and absolute liver weights ↑, relative and absolute adrenal gland weights ↑	BUA 1994; ECHA 2018
rat, no data	**30 days**, in the diet, 0, 0.02%, 0.1%, 0.5% (20, 100, 500 mg/kg body weight and day according to ECHA 2018)	**incomplete description of the study**; **20 mg/kg body weight**: "NOAEL"; **about 100 mg/kg body weight and above**: body weight gains ↓	BUA 1994; ECHA 2018
rabbit, no data	**5 weeks**, no data, 37 mg/kg body weight and day, 5 days/week	**37 mg/kg body weight**: "no noticeable damage", no other details	BUA 1994; ECHA 2018

5.2.3 Dermal application

The application of a 10% solution of cyanuric chloride in polyethylene glycol to the right ear of 4 male rabbits once a day on 10 consecutive days led to redness on the first day and to moderate swelling from day 3 onwards. If the solution was replaced by a 2% solution, no damage to the skin occurred (Nofer Institute of Occupational Medicine 1993 b).

Cyanuric chloride in petrolatum was applied under occlusive conditions to the dorsal skin of New Zealand White rabbits of both sexes in doses of 0, 50, 150 or 500 mg/kg body weight for 6 hours a day, on 5 days a week, for 21 days (Table 3). A group of control animals received the same treatment as the exposed animals, the only difference being that no substance was applied. Three male rabbits died during the study: 1 of the control animals, 1 animal from the middle dose group and 1 from the high dose group. Only the death of the animal in the middle dose group from severe multifocal ulcerative dermatitis was attributed to the substance. Discharge from the nose and eyes was observed in the animals of all dose groups. No unusual findings were noted on the skin of the untreated animals; mild erythema and very mild oedema were observed in the vehicle control group from exposure day 7 or 10 onwards. The severity of the findings in all treated animals increased with the number of applications and the dose. In comparison with the values determined at the beginning of the study, reduced body weights were noted in the males at doses of 150 mg/kg body weight and above and in the females at doses of 500 mg/kg body weight and day and above. The systemic NOAEL (no observed adverse effect level) was 50 mg/kg body weight; a local NOAEL was not determined (International Research and Development Corporation 1983 a).

Tab. 3 Effects induced by cyanuric chloride after repeated dermal application

Species, strain, number per group	Exposure	Findings	References
rabbit, Viennese White, 4 ♂	**10 days**, 2%, 10% (dose not specified), suspension in polyethylene glycol, treatment of right ear, left ear as control; daily	**10%**: erythema, from day 4 onwards: well circumscribed to moderate, no data for systemic effects	Nofer Institute of Occupational Medicine 1993 b
rabbit, New Zealand White, 6 ♂, 6 ♀	**21 days**, 0, 0, 50, 150, 500 mg/kg body weight and day, in petrolatum, occlusive, additional untreated control group, 5 days/week	**50 mg/kg body weight and above**: discharge from nose and eyes, severity of findings in skin increased with number of applications and dose, irritation, mild to moderate oedema and erythema at application site, pale areas of skin with cracks and abrasions, intraepidermal suppuration, dermal inflammation, epidermal and follicular hyperkeratosis and acanthosis, in 1/12: scabbing and scab tissue that was becoming detached, **systemic NOAEL (♂)**; **150 mg/kg body weight and above**: mortality ♂ (1/6, severe multifocal ulcerative dermatitis), severe erythema and oedema, body weights (♂) ↓; **systemic NOAEL (♀)**; **500 mg/kg body weight**: body weights ↓	International Research and Development Corporation 1983 a

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Cyanuric chloride (300 mg per animal) in polyethylene glycol was applied once under occlusive conditions to the intact or abraded dorsal skin of 6 Viennese White rabbits for a period of 24 hours using the method described in OECD Test Guideline 401. Erythema, swelling, erosion and necrosis of the skin which spread to areas of untreated skin were observed. The erythema score at the application site and the surrounding areas was 2.5 to 4 (on a scale with a maximum of 4). The erythema was severe for 5 days, then subsided until it was no longer noticeable after 11 days. The swelling subsided after 48 hours. Scabbing and then scars formed at the application site. The effects on the abraded skin did not differ greatly from those on the intact skin. Diffuse necrosis of the entire cutis and the upper part of the subcutis was observed in the skin of the animals (Nofer Institute of Occupational Medicine 1993 b).

The application of a 10% solution of cyanuric chloride in polyethylene glycol (dose not specified) on 1 ear of 4 rabbits once a day on 10 consecutive days caused redness on the first day and moderate swelling from day 3 onwards. A 2% solution did not induce local effects (Nofer Institute of Occupational Medicine 1993 b).

Six other studies reported irritation of the skin of rabbits and guinea pigs, which in some cases formed scabs during the observation period. In rabbits, 2 to 4 applications of 200 mg cyanuric chloride per animal induced corrosion and necrosis. Systemic effects were not observed in any of the studies (BUA 1994).

Conclusion: Cyanuric chloride has corrosive effects on the skin of rabbits.

5.3.2 Eyes

Cyanuric chloride was corrosive to the eyes of rabbits, leading to the discontinuation of a study after 4 days. The undiluted substance (0.1 g) was instilled into 1 eye of 1 male and of 1 female New Zealand White rabbit. The eye of 1 rabbit was rinsed with a physiological saline solution for 30 seconds after instillation of the substance; in this case, the initial findings were less severe. However, the same findings were observed in both of the treated eyes on day 4 after application: extensive opacity, insensitivity of the iris to light, and redness, swelling and discharge in the conjunctiva. In the unrinsed eye, the primary irritation index was 86 (on a scale with a maximum of 110) after only 24 hours and

remained at this level on the following 2 days. In the rinsed eye, the irritation index increased with time and was 34 after 24 hours, 39 after 48 hours, 59 after 72 hours and 84 after 96 hours. In all cases, the index was based on a scale with a maximum of 110. The effects on the cornea and iris increased in severity, those on the conjunctiva remained constant and were at the same level as those in the unrinsed eye on day 4 after application of the substance (Ciba-Geigy 1981).

After the instillation of 5 to 10 mg of cyanuric chloride in 1 eye of rabbits, superficial corneal defects and swelling of the conjunctiva were observed, which developed into purulent, non-necrotizing conjunctivitis and keratitis (BUA 1994).

Conclusion: Cyanuric chloride has corrosive effects on the eyes of rabbits.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

Positive results were obtained in a validation study for a local lymph node assay (LLNA) carried out with cyanuric chloride (purity not specified) in groups of 3 CBA/Ca mice (no other details) using a method that did not comply with OECD Test Guideline 429. The test substance (25 µl) was applied to the back of both ears of the animals on 3 consecutive days as a 2.5%, 5% and 10% formulation in acetone/olive oil (4:1). After removal of the lymph nodes and the determination of their weights, the lymphocytes were incubated with [^{3}H]-methylthymidine for 24 hours. In comparison with the control level of 1.0 cpm, the level of lymphocyte proliferation stimulated by the various concentrations was 63.2, 54.6 or 64.3 cpm, respectively. The mean lymph node weights were 7.7, 7.6 and 6.3 mg, respectively (Kimber and Weisenberger 1989). In other publications describing this test, the substance was applied as a 1%, 2.5% and 5% formulation in the same vehicle. [^{3}H]-Methylthymidine, however, was administered by intravenous injection. The lymphocytes were stimulated at proliferation levels of 21.8, 29.0 and 34.0, respectively (Ashby et al. 1995; Kimber et al. 1989).

A test protocol that was very similar to the above was chosen for a comparative study with groups of 3 Pirbright-White-Dunkin-Hartley guinea pigs and groups of 3 CBA/Ca mice. The guinea pigs were given 50 µl of the substance in dimethylacetamide/acetone/ethanol (4:4:3) as 0.5%, 1%, 2% and 5% test formulations and the mice were given 25 µl of the substance in acetone/olive oil (4:1) in the 3 lowest concentrations. The lymph nodes of the mice were prepared for examination on day 3, those of the guinea pigs on day 5. In comparison with the control animals treated with the vehicle, stimulation indices of 5.7, 5.8, 7.8 and 5.4, respectively (lymph node weights: 11.1 (control animals), 16.5, 28.1, 34.8 and 21.7 mg, respectively), were determined for the guinea pigs and stimulation indices of 13.0, 17.9 and 25.1, respectively, were determined for the mice. The lymph node weights for the mice were not reported (Maurer and Kimber 1991). Positive reactions were obtained in both species.

In a maximization test with groups of 10 female and 10 male Pirbright White guinea pigs, 19 of the 20 pre-treated animals produced positive reactions 24 hours after the challenge treatment with 0.05% cyanuric chloride in petrolatum; positive reactions were not obtained in any of the 20 control animals. The intradermal induction treatment was carried out with a 0.1% formulation of the test substance in propylene glycol/physiological saline solution and the topical induction treatment with a 0.5% formulation in petrolatum (ECHA 2018; Nofer Institute of Occupational Medicine 1994 b).

A positive result was obtained also in a maximization test with 12 female Hartley guinea pigs. In this test, the intradermal and topical induction treatments were carried out with 0.01% and 2% cyanuric chloride in polyethylene glycol 400, respectively. At the challenge with a 1% formulation of the substance in the same vehicle, all 12 pre-treated animals produced a reaction, but none of the 8 control animals (Nofer Institute of Occupational Medicine 1988).

In an earlier study that is not relevant for the evaluation, 8 Alderley Park guinea pigs were treated non-occlusively on both ears with 0.1 ml of a 10% formulation of cyanuric chloride in dimethyl formamide on 3 consecutive days. The challenge treatment was carried out on day 7 by applying 0.2 ml of a 1% formulation of cyanuric chloride to the shaved flank of the animals on an area 1 cm^2 in size. The erythematous reactions were severe in 1 animal, marked in 4 animals, weak in 1 animal and "just noticeable" in 2 animals. The report did not include more specific data for the control group (Stevens 1967).

5.4.1.1 In vitro studies

A comparative review of LLNA findings and test results from the U-SENS assay (myeloid U937 skin sensitization test; MUSST) lists cyanuric chloride as an "extreme sensitizer" with an EC3 value of 0.09%. Positive results were obtained with the substance in the U-SENS assay; however, an RPMI medium was used for the stock solution. An EC150 value of 15 µg/ml and a CV70 value of 68 µg/ml were determined in this assay (Piroird et al. 2015). This result is unusual because of the rapid hydrolysis of cyanuric chloride in aqueous media. Negative results were obtained in this assay with phthalic anhydride concentrations up to 200 µg/ml (using dimethyl sulfoxide as the vehicle for the stock solution).

In the GARD (genomic allergen rapid detection) assay, cyanuric chloride yielded negative results up to a concentration of 500 µM (Zeller et al. 2017). The results of this assay and what are considered positive findings from a preliminary study investigating the induction of gene expression for interleukin-8, haem oxygenase 1 and phorbol-12-myristate-13-acetate-induced protein 1 in peripheral THP-1 monocytes from human blood (Arkusz et al. 2010) are not included in the evaluation.

5.4.1.2 In chemico studies

A review of the findings obtained with 269 substances in the KeratinoSens assay, in the human cell line activation test (h-CLAT) and in the direct peptide reactivity assay (DPRA) included positive results obtained with the DPRA. However, to date, no tests appear to have been performed with the two other assays (KeratinoSens assay, h-CLAT). The DPRA carried out with cyanuric chloride demonstrated protein binding potency of 56% and 100% for the model peptide containing cysteine or lysine, respectively (Asturiol et al. 2016).

In another publication, a standard DPRA performed with cyanuric chloride revealed the depletion of model peptides containing lysine or cysteine by 99.3% and 74.1%, respectively (Lalko et al. 2012). Other studies that made use of the DPRA tested model peptides containing lysine, cysteine, histidine, tyrosine and arginine. Cyanuric chloride (purity 99%) led to the depletion of lysine, cysteine and histidine peptides by 100%, 79.8% and 99.0%, respectively. In these assays, cyanuric chloride was incubated in 10-fold excess (cysteine peptide) or 50-fold excess (other peptides) (Lalko et al. 2013).

5.4.2 Sensitizing effects on the airways

A report published by the Advisory Committee on Existing Chemicals of the German Chemical Society (BUA 1994) includes a lung sensitization test which did not reach a clear differential diagnosis for this end point.

In a preliminary, unvalidated mouse model for the induction of lymphocytic cytokine secretion by skin and respiratory tract-sensitizing substances, the increase in interleukin-4 and interleukin-10 levels after exposure to cyanuric chloride was similar to that determined after exposure to trimellitic anhydride and diphenylmethane-4,4′-diisocyanate. A corresponding increase in γ-interferon was not observed with any of the three substances. The contact allergens 2,4-dinitrochlorobenzene, isoeugenol and formaldehyde did not induce a marked increase in interleukin levels, but all led to a marked increase in the secretion of γ-interferon (Dearman et al. 1997).

For the induction treatment, 8 female Pirbright White guinea pigs were given 3 intradermal applications of cyanuric chloride as a 0.3% formulation in acetone. Each application consisted of 2 injections of 100 µl of the substance. The animals were treated at intervals of 2 days. This was followed by the challenge treatment with exposure of 4 animals on day 22 and 4 animals on day 24 to a cyanuric chloride concentration of 2.6 mg/m^3 for a period of 30 minutes. In preliminary studies, exposure to 3 mg/m^3 had been found to induce marked irritation. Provocation with 2.6 mg/m^3 led to effects in the pretreated animals similar to those observed in the control animals, possibly also because of an infection in the respiratory tract (no other details) (ECHA 2018).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

Studies were carried out with the sodium salt of the first hydrolysis product of cyanuric chloride, 4,6-dichloro-1,3,5-triazin-2(1H)-one, sodium salt (NHDT) (Table 4). As the local effect induced by this product is less severe, it can be administered in higher doses for the investigation of systemic effects.

In the preliminary study for an extended one-generation reproductive toxicity study, groups of 10 male and 10 female Wistar rats were given NHDT with the drinking water in concentrations of 0, 500, 1000 or 2000 mg/l (males: NHDT doses of 0, 45, 90, 140 mg/kg body weight and day; females: NHDT doses of 0, 60, 123, 200 mg/kg body weight and day). The males were exposed for 30 days, the females for about 51 to 57 days up to the birth of the offspring. The NOAEL for toxicity in the parent animals was 90 and 123 mg/kg body weight and day, respectively. The body weights of the parent animals and the number of implantations (without statistical significance) were reduced at 140 or 200 mg/kg body weight and day, respectively. Morphological changes in the reproductive organs were not observed. The viability, or survival following implantation, was reduced in the F1 generation (Charles River Laboratories 2018 b).

In an extended one-generation reproductive toxicity study carried out according to OECD Test Guideline 443, Wistar Han rats were given NHDT with the drinking water in concentrations of 0, 200, 600 or 2000 mg/l (target dose: 0, 16, 55, 160 mg/kg body weight and day); the males for 11 to 12 weeks, the females for 16 to 17 weeks. Reduced body weights, and follicular cell hypertrophy and ceroid changes in the thyroid gland were noted in the male parent animals at 160 mg/kg body weight and day. Extramedullary haematopoiesis and pigmentation in the spleen were observed in the males and females and the fertility index was reduced. In the offspring, body weights were reduced and total T4 levels increased. The NOAEL for fertility was 55 mg/kg body weight and day. At this dose level, the body weights and the creatinine levels in urine were reduced in the females, the total protein levels in urine and the liver weights were increased in the males and the total T4 levels were increased in the males and in the females. The NOAEL for the parental toxicity of NHDT was therefore 16 mg/kg body weight and day (Charles River Laboratories 2019). As the body weights of the offspring were reduced on postnatal days 1 and 4, the NOAEL for perinatal toxicity was 55 mg/kg body weight and day. There were no substance-induced effects on the gestation index, post-implantation index, litter size, sex ratio, index of living offspring, survival index and mortality up to postnatal day 4. No external malformations were noted.

Tab. 4 One-generation studies with 4,6-dichloro-1,3,5-triazin-2(1H)-one, sodium salt (NHDT) (sodium salt of the hydrolysis product of cyanuric chloride; its local effects are less severe, allowing for the use of higher doses)

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 10 ♂, 10 ♀	**0, 500, 1000, 2000 mg** NHDT/l **in the drinking water** (♂: 0, 45, 90, 140 mg/kg body weight and day; ♀: 0, 60, 123, 200 mg/kg body weight and day), 30 days (♂), 51–57 days (♀)	**preliminary study for a one-generation study** **90/123 mg/kg body weight**: **NOAEL for parental toxicity,** **parent animals**: slight reduction in feed consumption during gestation; **140/200 mg/kg body weight**: **parent animals**: feed consumption ↓ (♂ 7%, ♀ 5%), water consumption ↓ by up to 25% (♂ and ♀), body weight gains ↓ (♂: end of study 12%; ♀: immediately prior to mating 5%, end of gestation 15%, end of lactation 10%) without any signs of normalization of body weight, ♀: number of implantations not significantly ↓ (4/10 animals with only 4–9 implantations; control group 1/10 animals with 4 implantations, all others at least 10 implantations), mean number of implantations in all dose groups: 11.2 (0), 12.3 (45/60), 13.3 (90/123), 10.3 (140/200 mg/kg body weight)	Charles River Laboratories 2018 b

Tab. 4 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Wistar Han, F0: 25 ♂, 25 ♀; F1: 20 ♂, 20 ♀	**0, 200, 600, 2000 mg** NHDT/l **in the drinking water** (0, 16, 55, 160 mg/kg body weight and day)	according to OECD Test Guideline 443; **16 mg/kg body weight**: **NOAEL** for parental toxicity and F1; **55 mg/kg body weight**: **NOAEL for fertility and perinatal toxicity**; **55 mg/kg body weight and above: F0**: body weights and body weight gains ↓ (♀), mean corpuscular volume and haemoglobin ↓ (♂), total protein in urine ↑ (♂), creatinine levels ↓ (♀), total T4 ↑ (in ♂ only at this dose) without any effects on serum TSH, liver weights ↑ (♂), **F1**: no substance-induced effects; **160 mg/kg body weight**: **F0 systemic toxicity**: body weights ↓ (♂), feed consumption ↓ (♀), red blood cell count ↑ (♂) probably because of extramedullary haematopoiesis in the spleen, lymphocyte and red blood cell count and platelet distribution width ↓ (♀), creatinine levels ↓ (♂), follicular cell hypertrophy of the thyroid gland, kidney weights ↑ (♀), offspring: body weights ↓ on postnatal days 1 and 4, **F0 fertility**: fertility index ↓ possibly caused by reduction in body weights (♀, 79%) **F1 after lactation**: **16 mg/kg body weight and above**: body weights ↓ (♂); **55 mg/kg body weight and above**: body weights ↓ (♀), total T4 ↑ but all other values for the thyroid gland within the normal range of variation, follicular cells in the ovaries ↓ but not in the corpora lutea and without any effect on reproduction parameters; **160 mg/kg body weight**: body weight gains ↓ (♂), red blood cell distribution width and mean corpuscular volume ↓ (♂), potassium in the blood ↓ (♂), reticulocytes ↑ (probably because of extramedullary haematopoiesis) and pigmentation in the spleen **F1 during lactation**: **160 mg/kg body weight**: body weights ↓, probably caused by the reduction in F0 body weights (♀) during gestation, no compensation for lower body weights during entire lactation phase, total T4 ↑ on postnatal days 22–24, levels within the range of historical control values ⟶ not adverse	Charles River Laboratories 2019

PND: postnatal day; T4: thyroxine; TSH: thyroid-stimulating hormone

5.5.2 Developmental toxicity

The studies investigating this end point are shown in Table 5.

In a developmental toxicity study with gavage doses given to CD rats, an increased number of post-implantation losses was observed at the low dose of 5 mg/kg body weight and day and above that was not statistically significant. At the high dose of 50 mg/kg body weight and day the effect was just barely significant. At this dose the number of living offspring was reduced. Excessive salivation and rattling breathing sounds were noted in the dams, but no substance-induced systemic histopathological findings. No substance-induced effects were observed in the offspring (International Research and Development Corporation 1983 b). Microphthalmia (small/rudimentary eyeball) was noted in 1 foetus in each dose group and 1 case of cleft palate was found in the middle dose group. Overall, both the post-implantation losses and the incidence of microphthalmia at 5, 25 and 50 mg/kg body weight and day were still within the range of the historical controls of the laboratory. For this reason, these findings are not regarded as having been induced by the substance and the high dose of 50 mg/kg body weight and day is considered the NOAEL for developmental toxicity.

A dose-finding study for a developmental toxicity study was carried out according to OECD Test Guideline 414 in dose groups of 6 female New Zealand White rabbits. The animals were given NHDT with the drinking water in concentrations of 0, 1800, 3500 or 7500 mg/l (0, 100, 160, 288 mg/kg body weight and day) from gestation days 6 to 29. As in the high dose group feed and water consumption and body weight gains were reduced and two litters were born

prematurely, the NOAEL for the dams was the middle dose of 160 mg/kg body weight and day. The decrease in foetal body weights was not dependent on the dose (Charles River Laboratories 2018 a).

The developmental toxicity study was carried out according to OECD Test Guideline 414 in dose groups of 22 New Zealand White rabbits. The animals were given NHDT with the drinking water in concentrations of 0, 640, 1600 or 4000 mg/l (0, 39, 101, 227 mg/kg body weight and day) from gestation days 6 to 29. During the first days of substance administration, losses in body weight were observed in the dams of the high dose group, followed by reduced body weight gains. Reduced body weight gains were observed also in the dams of the middle dose group. In part, this was attributed to the taste of the substance. As was to be expected, litter sizes correlated inversely with mean foetal weights. No substance-induced findings were observed in the foetuses. Therefore, the NOAEL for developmental toxicity was 227 mg/kg body weight and day. The NOAEL for maternal toxicity was 39 mg/kg body weight and day (Charles River Laboratories 2018 a).

The extended one-generation reproductive toxicity study in rats that was carried out according to OECD Test Guideline 443 and described in the preceding section determined a NOAEL for perinatal toxicity of 55 mg/kg body weight and day (Charles River Laboratories 2019). This value was based on the reduced body weights of the offspring on postnatal days 1 and 4.

Tab. 5 Developmental toxicity studies with cyanuric chloride and 4,6-dichloro-1,3,5-triazin-2(1H)-one, sodium salt (NHDT) (sodium salt of the hydrolysis product of cyanuric chloride; its local effects are less severe, allowing for the use of higher doses)

Species, strain, number per group	Exposure	Findings	References
rat, COBS CD, 25 pregnant ♀	**0, 5, 25, 50 mg cyanuric chloride/kg body weight and day** in mineral oil, GD 6–19, gavage, necropsy on day 20	**5 mg/kg body weight and above**: **dams**: post-implantation losses/litter not significantly ↑: 0.8, 1.2, 1.2, 1.4 at 0, 5, 25, 50 mg/kg body weight[a)]; **foetuses**: 1 animal with microphthalmia[b)]; **25 mg/kg body weight**: **dams**: 1 animal died because of an intubation error, **foetuses**: 1 animal with a cleft palate (not substance-induced), 1 animal with microphthalmia[b)]; **50 mg/kg body weight**: **NOAEL for developmental toxicity**; **dams**: dry matter around the face, front legs and anogenital region, dull fur, excessive salivation, rattling breathing sounds, slight reduction in mean body weight gains (126 g, 121 g, 123 g, 108 g at 0, 5, 25, 50 mg/kg body weight), no substance-induced systemic histopathological findings, post-implantation losses significantly ↑; **foetuses**: number of living foetuses not significantly ↓[c)], 1 animal with microphthalmia[b)]	International Research and Development Corporation 1983 b
rabbit, New Zealand White, groups of 6 ♀	**0, 1800, 3500, 7500 mg NHDT/l in the drinking water** (0, 100, 160, 288 mg/kg body weight and day), GD 6–29, necropsy on day 29	body weight gains ↓, decrease not dose-dependent; **160 mg/kg body weight**: **NOAEL for maternal toxicity**; **288 mg/kg body weight**: **dams**: orange-coloured urine, feed and water consumption ↓, 5% loss in body weight up to day 9 after mating, then body weight gains ↓, 2 animals with premature litters (day 27 and day 29, dead foetuses found in litters); foetal weights reduced in all dose groups, but within the historical control values: 9% (100 mg/kg body weight), 5% (160 mg/kg body weight), 11% (288 mg/kg body weight)	Charles River Laboratories 2018 a

Tab. 5 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rabbit, New Zealand White, groups of 22 ♀	**OECD Test Guideline 414 0, 640, 1600, 4000 mg NHDT/l in the drinking water** (0, 39, 101, 227 mg/kg body weight and day), GD 6–29, necropsy on day 29	**39 mg/kg body weight**: **NOAEL for maternal toxicity**; **dams**: feed consumption reduced by up to 20% on days 12–15 after mating – not adverse; **101 mg/kg body weight**: **dams**: body weight gains ↓, feed consumption reduced by up to 40% until day 18 after mating; **227 mg/kg body weight**: **NOAEL for developmental toxicity**; **dams**: 2% loss in body weight until day 9 after mating, then body weight gains ↓, feed consumption reduced by up to 40% until day 18 after mating, water consumption ↓; no unusual findings in the foetuses	Charles River Laboratories 2018 a

historical laboratory controls:
[a] post-implantation losses/litter: 0.8 (0.3–1.6)
[b] anophthalmia or microphthalmia: 8/21186 foetuses (0–1.2%), 8/1579 litters (0–4.5%)
[c] living foetuses/litter: 13.3 (10.5–15.7)
GD: gestation day

5.6 Genotoxicity

5.6.1 In vitro

Cyanuric chloride was not found to be mutagenic in the Salmonella typhimurium strains TA97a, TA98, TA100 and TA102 up to concentrations of 500 µg/plate both with and without the addition of a metabolic activation system from rat liver. At concentrations of 100 µg/plate and above, the growth of the bacterial strain TA97a was slightly reduced without metabolic activation, which is regarded as evidence that cyanuric chloride induces cytotoxic effects. The study was carried out according to OECD Test Guideline 471 (Nofer Institute of Occupational Medicine 1994 a).

In another study, cyanuric chloride was not found to be mutagenic in the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and Escherichia coli WP2 uvrA at concentrations up to 5000 µg/plate both with and without the addition of a metabolic activation system from the rat liver. In both tests, precipitation occurred at the two high concentrations with normal levels of background growth. The positive controls produced the expected results (Envigo 2016).

Also in another study, cyanuric chloride was not found to be mutagenic in the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 both with and without the addition of a metabolic activation system from the rat liver (concentration not specified; BUA 1994).

In a $TK^{+/-}$ mutation test carried out in L5178Y mouse lymphoma cells according to OECD Test Guideline 476 (the valid test guideline at the time of the study), cyanuric chloride was not found to be mutagenic up to the highest concentration tested of 25 µg/ml after exposure periods of 3 and 24 hours and both with and without the addition of a metabolic activation system from rat liver. The ratio of small to large colonies remained unchanged. Complete cytotoxicity (low survival incidence) was observed at a concentration of 50 µg/ml; the positive controls produced the expected results (Laboratory of Pharmacology and Toxicology 2012). Since 2016, this test has been included in the updated OECD Test Guideline 490.

5.6.2 In vivo

In a micronucleus test carried out in the bone marrow of mice according to OECD Test Guideline 474 with a single gavage dose of cyanuric chloride in arachis oil at the maximum tolerable dose of 619 mg/kg body weight, the substance was not found to induce clastogenic effects after 24, 48 and 72 hours. In the exposed animals, a very slight decrease

in the ratio of polychromatic to normochromatic erythrocytes was observed. Four animals died. The positive control cyclophosphamide induced the expected marked increase in micronuclei (Degussa 1987).

5.7 Carcinogenicity

Two studies in rats carried out in 1966 observed tumours only in the range of spontaneous variability. The choice of rat ("white, not purebred"), the insufficient number of rats per sex and dose group (n = 23–27) and the study procedure with either subcutaneous application of 10 mg of cyanuric chloride per animal once a week or oral doses of 10 mg per animal in sunflower oil on 6 days a week were not considered suitable for the evaluation of potential carcinogens (BUA 1994).

5.8 Other effects

In a study of the antigen-antibody reaction of immunized rabbits to immunosuppressive agents, cyanuric chloride changed a number of affinity parameters. However, the test did not provide evidence of direct immunotoxic effects (BUA 1994).

A "changed immunological reactivity" in workers exposed to cyanuric chloride could not be evaluated because the information included in the report was incomplete (BUA 1994).

6 Manifesto (MAK value/classification)

The critical effects of cyanuric chloride are irritation of the eyes and respiratory tract of humans and animals.

MAK value. A retrospective cohort study is available of 427 male employees who had worked at 3 cyanuric chloride production plants for at least 12 months between 1958 and 2007. The study report included 67 values that had been determined analytically. The exposure data were extrapolated based on a job-exposure matrix. A probable effect on the FEV_1 was determined after exposure to cyanuric chloride at levels > 0.01 ml/m³ (0.08 mg/m³) (Evonik Technology & Infrastructure GmbH 2018; Morfeld et al. 2014; Morfeld and Noll 2014). There are no data for irritation of the upper respiratory tract. Overall, the findings of the study are difficult to interpret (Section 4.2). For this reason, a MAK value cannot be derived from this study and the findings from animal studies are used for this purpose.

In a 90-day inhalation study with whole-body exposure of rats, a slight increase in the inflammatory cells in the nose without changes in the mucosa was observed in individual males in all concentration groups. In addition, foamy macrophages and infiltration of lymphocytes in the alveolar septa were observed in the high concentration group at an exposure level of 0.032 ml/m³ (cyanuric chloride vapour concentration of 0.25 mg/m³). The findings may have been influenced by a simultaneously occurring infection (Nofer Institute of Occupational Medicine 1994 c, 1997). On the basis of the study description, it is not possible to determine with certainty whether the effects were induced by the substance (Section 5.2.1). The Commission has derived a LOAEC of 0.032 ml/m³ (cyanuric chloride vapour concentration of 0.25 mg/m³), making the next-lower concentration of 0.0065 ml/m³ (0.05 mg/m³) the NOAEC.

On the basis of the NOAEC of 0.0065 ml/m³ from the 90-day inhalation study and taking into consideration the extrapolation of the findings from animal studies to humans according to the method developed by Brüning et al. (2014) (1:3), a possible intensification of the effects over time (1:2) and the preferred value approach, a MAK value of 0.001 ml/m³ (0.0076 mg/m³) has been established.

The findings of the retrospective cohort study of workers with cyanuric chloride exposure (Evonik Technology & Infrastructure GmbH 2018; Morfeld et al. 2014; Morfeld and Noll 2014) do not contradict the MAK value of 0.001 ml/m³ (0.0076 mg/m³) derived for cyanuric chloride on the basis of findings from animal studies; this value is still below the odour threshold in humans of about 0.02 mg/m³.

Peak limitation. As irritation was decisive for the derivation of a MAK value, the substance has been classified in Peak Limitation Category I. No valid data are available for the irritation threshold; however, an excursion factor of 2 has been established because the odour threshold is about 0.0025 ml/m^3 (0.02 mg/m^3).

Prenatal toxicity. In the oral developmental toxicity study in rats, the post-implantation losses and the incidence of microphthalmia induced at dose levels of 5, 25 and 50 mg/kg body weight and day were still within the range of the historical controls of the laboratory. For this reason, the high dose of 50 mg/kg body weight and day is regarded as the NOAEL for developmental toxicity. In a developmental toxicity study in which doses of 4,6-dichloro-1,3,5-triazine-2(1H)-one, sodium salt (NHDT), the sodium salt of the hydrolysis product of cyanuric chloride, were given to rabbits in the drinking water, no toxic effects on development were induced up to the highest dose tested of 227 mg/kg body weight and day. In the dams, body weight gains were reduced; this effect was in part attributed to the taste of the substance. A NOAEL for perinatal toxicity of 55 mg/kg body weight and day has been derived based on the findings of an extended one-generation study, as the body weights of the offspring were reduced at the high dose of 160 mg/kg body weight and day on postnatal days 1 and 4.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAELs of 50 (developmental toxicity) and 55 mg/kg body weight and day (perinatal toxicity) in the rat and of 227 mg/kg body weight and day in rabbits (developmental toxicity) to a concentration in workplace air: the corresponding species-specific correction values (rat: 1:4, rabbit: 1:2.4), the assumed oral absorption of 100%, the body weight (70 kg) and the respiratory volume (10 m^3) of the person and the assumed 100% absorption by inhalation. The concentrations calculated from this are 87.5, 135 and 662 mg/m^3. As the 11 513, 17 763 and 87 105-fold margins between the calculated NAECs (no adverse effect concentrations) and the MAK value of 0.001 ml/m^3 (0.0076 mg/m^3) are sufficiently large, cyanuric chloride has been classified in Pregnancy Risk Group C.

Carcinogenicity. No valid carcinogenicity studies are available. The substance has not been classified in any of the categories for carcinogens.

Germ cell mutagenicity. Cyanuric chloride was not found to be mutagenic in the Salmonella typhimurium strains TA97a, TA98, TA100, TA102, TA1535, TAG1537 and in Escherichia coli WP2 uvrA or in the TK$^{+/-}$ mutation test with L5178Y mouse lymphoma cells both with and without the addition of metabolic activation. Clastogenic effects were not determined in a micronucleus test in the bone marrow of mice given oral doses of the substance. No studies that investigated germ cells are available. The substance has not been classified in one of the categories for germ cell mutagens.

Absorption through the skin. Cyanuric chloride is severely irritating to the skin. Direct contact of the skin of animals with the undiluted substance caused marked local damage. In addition, cyanuric chloride breaks down to cyanuric acid and hydrochloric acid upon contact with water. As a result, penetration of the substance through the skin is not to be expected at a level of exposure that is tolerable to the skin. For this reason, cyanuric chloride has not been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. The clinical findings in humans are not sufficient to evaluate the skin sensitization potential of cyanuric chloride. However, several positive results in local lymph node assays, which were not yet carried out according to OECD test guidelines, and positive results in maximization tests with guinea pigs are regarded as evidence of a marked sensitizing potential for cyanuric chloride. For this reason, cyanuric chloride has been designated with an "Sh" (for substances which cause sensitization of the skin).

With regard to allergenic effects in the airways, other than evidence of specific IgE, there are no reliable clinical findings of allergic respiratory diseases induced by cyanuric chloride. Findings determined in animals under experimental conditions do not allow the assumption of the same kind of effects in humans. For this reason, cyanuric chloride, though suspected of having airway-sensitizing potential, has not been designated with "Sa" (for substances which cause sensitization of the airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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