Substance Name: glutaral

EC Number: 203-856-5

CAS Number: 111-30-8

MEMBER STATE COMMITTEE SUPPORT DOCUMENT FOR IDENTIFICATION OF

GLUTARAL

AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS RESPIRATORY SENSITISING PROPERTIES (ARTICLE 57(F) - HUMAN HEALTH) PROPERTIES

Adopted on 3 June 2021

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IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

Substance name: glutaral (glutaraldehyde)

EC number: 203-856-5

CAS number: 111-30-8

- Glutaral is identifiedas a substance of equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of Regulation (EC) No 1907/2006 (REACH) according to Article 57(f) of REACH Regulation.

Note – throughout this report the substance glutaral (glutaraldehyde) is referred to as glutaraldehyde or the abbreviation GA.

Summary of how the substance meets the criteria set out in Article 57 of the REACH Regulation

Glutaraldehyde is covered by index number 605-022-00-X of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3 (the list of harmonised classification and labelling of hazardous substances) and it is classified, amongst various other hazards, as a respiratory sensitiser (Resp. Sens. 1).

Glutaraldehyde is identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with respiratory sensitising properties for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 of the REACH regulation.

Evidence that the substance is of an equivalent level of concern includes:

Sensitisation is an irreversible malfunction of the immune system which leads to a permanently increased risk of serious adverse health effects. There are numerous studies on workers who became sensitised to GA and developed occupational asthma (OA). Asthma is a serious health effect that may result in permanent impairment of lung function. It has been reported that ex-employees with previous GA exposure have significantly lower lung function than current employees. Asthma may also have fatal effects.

Most studies on the effects of GA describe both an early onset (type I) and a late phase (delayed) asthmatic response. Several studies report an increase of IgE antibodies specific to GA both in humans and in mice after inhalation exposure to GA.

Symptoms of respiratory tract sensitivity have been shown to arise after variable periods of workplace exposure. Studies report symptoms appearing from 3 months up to 23 years from the first exposure to GA. In addition, the typical non-specific symptoms of GA-associated asthma (chest tightness, persistent cough, and wheezing) have been coupled with a delay in symptoms after exposure and may lead to a delayed diagnosis. If the symptoms cannot be immediately coupled to the exposure, there is a risk that exposure will continue and that the asthma will be further aggravated, leading to irreparable damage to lung function.

In addition to its respiratory sensitising properties, GA is a strong skin sensitiser with a harmonised classification as Skin Sens. category 1A. It has been indicated that skin exposure and skin sensitisation to GA may be of importance for respiratory sensitisation.

Long-term illness, such as asthma or impairment of lung function as a result thereof, limits the possibility of living a normal working and private life. Asthma may indeed require long-term medication. Sensitised individuals may need to change workplace and profession and retraining of affected staff may be required.

Several studies have investigated the cost implications of respiratory sensitisation for society in terms of e.g., healthcare, retraining, production losses (due to e.g., sick leave and reduced work capability) and impaired quality of life. There are also data on the economic or societal costs attributed to GA-induced OA that demonstrate large costs for the society.

There is currently no established method to determine a safe concentration for respiratory hypersensitivity, or data suitable to define such thresholds for GA. The difficulty to derive a safe exposure level is illustrated by (i) well-documented reports on cases of OA caused by GA where allergic reactions in the airways have been reported at low exposure levels and (ii) variable national and international occupational exposure limits primarily based on respiratory effects.

Considering the type and severity of the health effects mentioned above, the delay and irreversibility of such effects, their impacts on the person's quality of life and the overall societal concern and costs, GA can be regarded as giving rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 of the REACH regulation.

Registration dossiers submitted for the substance: Yes

Justification

1. Identity of the substance and physical and chemical properties

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	203-856-5
EC name:	Glutaral
CAS number (in the EC inventory):	111-30-8
CAS number: Deleted CAS numbers:	107950-89-0 1428979-54-7 1497435-71-8 37245-61-7 79215-57-9
CAS name:	Pentanedial
IUPAC name:	glutaraldehyde
Index number in Annex VI of the CLP Regulation	605-022-00-X
Molecular formula:	C5H8O2
Molecular weight range:	100.12 g/mol
Synonyms:	1,5-pentanedial glutar aldehyde pentane-1,5-dial 1,5-pentanedione

Structural formula:

1.2 Composition of the substance

Name: glutaral (glutaraldehyde)

Description: n/a

Substance type: mono-constituent

Due to its high reactivity, glutaraldehyde is typically available as an aqueous solution containing up to 50% glutaraldehyde by weight. Glutaraldehyde may also be available in other media besides water.

1.3 Physicochemical properties

Table 2: Overview of physicochemical properties[1]

Property	Description of key information	Value [Unit]
Physical state at 20°C and 101.3 kPa	Colourless liquid	
Melting/freezing point	Peak maximum ca. -18 Extrapolated onset temperature ca. -33; range about -50 to -15 -18 to -21.2 (performed at atmospheric pressure)	°C
Boiling point	101.5 101.95 100.7	°C at 987.1 hPa °C at 1013.25 hPa °C at 1013 hPa
Relative density	1.129	kg/dm3
Vapour pressure	44	Pa (20 °C, 100% GA)
Surface tension	ca. 68 72.4	mN/m at 20 °C (0.2% aqueous preparation of the test item corresponds to a 0.1% solution of pure glutaraldehyde) mN/m at 20 ºC (1g/l corresponding to 0.5 g/l or 0.05% solution of pure glutaraldehyde)
Viscosity	12.75 20.15 4.72	mm2/s at 25 °C mPa/s at 20 °C mPa/s at 40 °C
Water solubility	GA is an aqueous solution and as such is fully soluble (≥ 51.3 g glutaraldehyde/100 ml)	
Partition coefficient n-octanol/water (log value)	logPow -0.41 logPow -0.36 logPow -0.80 logPow -0.33	pH 5, temp. 23 +/- 1 °C pH 7, temp. 23 +/- 1 °C pH 9, temp. 23 +/- 1 °C at 25 °C, pH not reported
Flash point	No flashpoint was observed for either sample at temperatures up to 95 °C	

[1] ECHA (2013). CLH report for glutaraldehyde. Proposal for Harmonised Classification and Labelling.

2. Harmonised classification and labelling

Glutaraldehyde is covered by Index number 605-022-00-X in part 3 of Annex VI to the CLP Regulation as follows:

Table 3: Classification according to Annex VI, Table 3 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)	Pictogram, Signal Word Code(s)	Hazard statement code(s)	Suppl. Hazard statement code(s)		
605-022-00-X	glutaral; glutaraldehyde; 1,5-pentanedial	203-856-5	111-30-8	Acute Tox. 2 Acute Tox. 3 STOT SE 3 Skin Corr. 1B Resp. Sens. 1 Skin Sens. 1A Aquatic Acute 1 Aquatic Chronic 2	H330 H301 H335 H314 H334 H317 H400 H411	GHS06 GHS05 GHS08 GHS09 Dgr	H330 H301 H335 H314 H334 H317 H410	EUH071	STOT SE 3; H335: 0,5% ≤ C < 5% M= 1	

For skin- and respiratory sensitisation, classification into sub-categories (1A or 1B) is required when data are sufficient. Since there are no formally recognised and validated animal or *in vitro* tests for respiratory sensitisation, classification is typically made based on human data (i.e. case reports, epidemiological studies, medical surveillance, reporting schemes). High frequency of occurrence in humans (category 1A) and low to moderate frequency of occurrence in humans (category 1B) cannot be defined as specific concentrations or percentages for human study data, because, when considering human evidence, it is necessary to consider the size of the exposed population and the extent and conditions of exposure, including frequency. Such data are rarely available. This is reflected by the fact that, in the EU, no substance has yet been sub-categorised for respiratory sensitisation. Consequently, all five respiratory sensitisers currently included in the Candidate list have a harmonised classification as Resp. Sens. category 1.

3. Environmental fate properties

Not relevant for the identification of the substance as SVHC in accordance with Article 57(f) of REACH.

4. Human health hazard assessment

4.1 Sensitisation

Sensitisation is a malfunction of the immune system which leads to a permanently increased risk of serious adverse health effects. It includes two phases: the first is induction of specialised immunological memory in an individual by exposure to an allergen. For the most part, this is an asymptomatic event. The second event is elicitation, i.e., production of an allergic response by exposure of a sensitised individual to the same allergen (ECHA, 2017). Once sensitised, an allergic reaction can occur whenever the individual is re-exposed to the allergen. Elicitation generally occurs at much lower concentrations of the allergen than induction.

In the case of respiratory sensitisation, the allergic response may be early onset or late phase. A rapid immune response (type I) is mediated by preformed antigen-specific IgE antibodies and subsequent mast cell degranulation. This causes the release of histamine and other mediators causing inflammation and swelling commonly associated with immediate hypersensitivity, such as bronchoconstriction in asthma. If these mediators are released in sufficient quantities, as well as systemically, this may lead to anaphylactic shock. Other mechanisms of hypersensitivity cause late-phase responses and involve tissue damage following the binding and cross-linking of antigen-specific antibodies to targets (type II and III) or are solely cell-mediated (type IV hypersensitivity reactions). Asthma employs one or more of these mechanisms concurrently, whereas skin sensitisation is a typically reported as a type IV hypersensitivity reaction.

Occupational asthma (OA) is growing in prevalence worldwide. De Matteis and co-workers (2017) describe an incidence of approximately two to five cases of OA per 100,000 population each year, or about 15 to 20 percent of the overall adult-asthma burden. GA is often included among substancesreported in surveillance systems for OA, e.g., it was responsible for 6% of the reported cases in the Shield reporting scheme in the UK (Diar Bakerly et al. 2008). The actual number of cases is probably higher due to the under-recognised and unreported incidents (Blanc and Toren, 1999; Baur et al. 2012).

GA has a harmonised classification as a respiratory sensitiser in category 1 and as skin sensitiser in category 1A in CLP (ECHA, 2014). There are many scientific publications that report effects of GA on the respiratory system and the skin. A selection of representative studies has been summarised below. These studies are chosen with the specific aim of providing information for the identification of GA as an SVHC according to Article 57f of the REACH Regulation.

4.1.1 Skin

Skin exposure and sensitisation may be of importance for respiratory sensitisation, as respiratory sensitisation may be induced not only by inhalation but also by skin contact (ECHA, 2017; Dotson *et al.*,2015). Hence, the strong skin sensitising property of GA is also of importance since it may result in heightened respiratory responsiveness following inhalation exposure.

4.1.1.1 Non-human information

The dose-response relationship between GA exposure and the development of T cell-mediated versus IgE-mediated responses was studied in CBA and BALB/c mice. The sensitising potential of GA was explored using the local lymph node assay (LLNA) at concentrations ranging from 0.75% to 2.5%. A concentration-dependent increase in lymphocyte proliferation was observed with EC3 values of 0.072% and 0.089% (hence indicating a strong sensitiser, ≤2%). The mouse ear swelling test was used to evaluate the potential for GA to elicit IgE- and contact hypersensitivity responses. In animals induced and challenged with 2.5% GA an immediate response was seen, whereas animals induced with 0.1% or 0.75% and challenged with 2.5% GA exhibited a delayed response. Only the 2.5% exposed group demonstrated a significant increase of IgE+B220+ cells and serum IgE. Furthermore, following 3 days of dermal exposure, a

significant increase in IL-4 mRNA in the draining lymph nodes was observed only in the 2.5% exposed group. These results indicate that the development of an immediate versus a delayed hypersensitivity response following dermal exposure to GA is at least in part mediated by the exposure concentration (Azadi *et al*., 2004).

A study by van Triel and coworkers (2011) tested GA in skin and respiratory LLNAs to explore if structurally related aldehydes caused similar effects. In a study previously performed by the authors, formaldehyde tested negative for sensitisation by inhalation and positive in the skin LLNA. Thus, BALB/c mice were exposed by inhalation to 25 mg/m3 or 74 mg/m3 GA, both as a vapour and as an aerosol in a respiratory LLNA. Other groups of mice were dosed with 0.25% or 2.5% GA on the dorsal area of the ears (skin LLNA). Lymphocyte proliferation and cytokine production were measured in the draining lymph nodes. GA was positive in the skin LLNA but inhalation exposure to GA did not result in an immunological response, despite comparable tissue damage (irritation) in the skin and respiratory tract. According to the authors, this could indicate that sensitisation of the airways to GA is mediated through skin exposure. It should, however, be noted that the LLNA for respiratory sensitisation is not a validated test method, and that the lack of a positive response may be due to that the test system is not optimised to detect respiratory sensitisation.

4.1.1.2 Human information

In the information network of dermatological clinics (IVDK), a total of 56,170 patients were patch-tested in the years 2014 to 2018. Overall, 16,807 of these patients (29.9%) suffered from hand eczema, of which 7,725 (46.0%) had occupational dermatosis (OD) and 6,820 (40.6%) had no OD. For the remaining patients, the link between hand eczema and occupational exposure was unknown. In this study, GA was reported as a common allergen in hand eczema patients with OD. To conclude, the clinical data support the skin sensitising property of GA, and indicate it is a frequently reported skin allergen (Mahler and Dickel, 2019).

A total of 4,238 patients were patch-tested in a standardised manner with a series of 70 allergens at the North American Contact Dermatitis Group from 2011 to 2012 (Warshaw *et al*., 2015). As compared with previous reporting periods (2009-2010 and 2000-2010), positive reaction rates statistically increased for 6 allergens, of which GA was one of the most common with 1.5% positive test results.

In a 5-year study at the University of Kansas dermatology clinics, 468 patients were tested for skin sensitisation to GA in a skin patch test (Shaffer and Belsito, 2000). Out of these, 17 subjects were found to be positive (3.6%). Among the tested patients there were 51 health care workers and 9 of these were positive (17.6%), while among the non-health care workers there were only 8 positive cases from 417 (1.9%). Hence, GA exposure caused skin sensitisation in nearly one fifth of the tested health care workers, being the most common positive test result among the chemicals tested. A higher-than-expected co-reactivity between GA and formaldehyde was also found among cases, which could not be explained by concomitant exposure. The study summarised several reports where allergic contact dermatitis from GA caused persistent dermatitis, which frequently forces workers to leave their job.

Allergic contact dermatitis to GA was found in 13 health-care workers with hand dermatitis (Nethercott *et al*., 1988). Cross-reactivity to other chemicals was noted in 10 subjects. The eruption persisted for more than 6 months in 10 subjects. In 5 cases, the skin disease forced the worker to leave his occupation.

4.1.2 Respiratory system

4.1.2.1 Non-human information

A mouse IgE test was performed to assess the potential for respiratory sensitisation of GA (Kimber 1994, reviewed in the GA CLH dossier, ECHA, 2013). The test was based on the hypothesis that IgE levels are not changed by skin sensitising substances but rise during respiratory sensitisation and that elevated IgE levels correlate with a higher risk of asthma. Groups of six BALB/c male mice were dosed dermally with GA concentrations of 0, 2.5, 5 and 12.5%. Seven days later, GA at half of the initial concentration was applied to the dorsum of both ears. Fourteen days later the animals were sacrificed and the concentration of serum IgE was determined. Results were compared to a positive (25% trimellitic anhydride) and a negative (1% DCNB; a known contact sensitiser that does not induce respiratory sensitisation) control. GA gave a clear dose-dependent IgE response, supporting the evidence of its respiratory sensitising properties through an IgE-mediated response.

4.1.2.2 Human information

In a study by Gannon *et al*. (1995) seven of eight workers from endoscopy or x-ray departments, exposed to GA, underwent serial peak expiratory flow (PEF) measurements, all of which showed a pattern indicating OA. The subjects included had a history of asthmatic symptoms that improved when away from work. In addition, one subject had pre-existing asthma and 2 cases showed positive skin tests to common allergens. Subjects had been exposed to GA from 6 months to 23 years prior to onset of symptoms suggestive of OA. Breathing zone samples were collected during simulated specific bronchial challenge tests with 2% GA, which ranged from 0.064 to 0.081 mg/m3, with a median airborne GA level of 0.068 mg/m3. OA was diagnosed when asthmatic symptoms occurred in relation to GA exposure and improved when away from exposure, and when the effect of exposure was also documented on serial two hourly PEF measurements. OA due to GA was also diagnosed if exposure to low levels of GA during controlled specific bronchial challenge tests resulted in a 15% or more fall in forced expiratory volume in one second (FEV1) compared with values at a similar time following saline challenge. In addition to the above, thirty personal air samples were collected from 13 hospital endoscopy units to estimate GA exposure levels at workplace. For personal short-term exposure the median GA concentration was 0.16 mg/m3. Short term measurements are more likely to capture peak levels of GA vapour compared to long term samples. For personal long-term samples, the median GA level was 0.041 mg/m3, for static short-term samples the median level was 0.17 mg/m3. GA concentrations in 19 air samples collected from 6 x-ray darkrooms were lower than 0.009 mg/m3. The low levels in air samples suggest that elicitation of asthma may appear at very low levels. In this study it was found that three of the workers also tested positive to formaldehyde in a bronchial challenge, suggesting cross-reactivity between the two substances (Gannon *et al*., 1995).

Palczyński *et al*. (2001) studied 11 workers with OA due to GA, 10 non-exposed atopic patients with perennial asthma and rhinitis, and 10 non-exposed healthy subjects to evaluate changes in nasal lavage fluid content before and after GA challenge exposure. Workers with asthma had been exposed to GA for 6 ± 3.2 years. Upon GA challenge, workers diagnosed with OA had significantly increased eosinophil numbers and concentrations of albumin, eosinophil cation protein, and mast-cell tryptase in the nasal lavage fluid. These results indicate an immunologic mechanism for GA-induced asthma. The mean concentration of GA in air during the challenge was 0.32±0.08 mg/m3. All the subjects with OA included in the study had a late-phase asthmatic reaction after GA-challenge, and three of these subjects had an additional early reaction within 30 minutes after exposure. This further supports an immunological mechanism of GA-induced asthma.

Another study evaluated bronchoalveolar lavage fluid (BALF) components and Clara cell protein (CC16) concentration in serum and BALF before and after GA inhalation challenge (Palczyński et al. 2005). Twenty-four hours post challenge, significantly lower CC16 levels in BALF and serum

were demonstrated and significantly increased proportions of eosinophils, basophils, and lymphocytes in BALF of the GA-sensitised asthmatics were detected, which are signs of an inflammatory response. Mean air concentration of GA during the provocation test was 0.38 mg/m3 (range 0.23 to 0.4 mg/m3).

Di Stefano *et al*. (1999) studied 24 healthcare workers with respiratory symptoms (cough, chest tightness, and wheezing) related to GA exposure, which improved on days away from work. All of them presented a time interval between first exposure to GA and onset of respiratory symptoms suggestive of OA (mean 6.7 years; range 1 to 20 years). In 10 of them (41.6%), the onset of cough, chest tightness, and wheezing was preceded by nasal symptoms (stuffiness, rhinorrhea, and sneezing) related to GA exposure for a variable interval of time (mean 5.3 years; range 6 months to 10 years). Specific bronchial provocation tests for diagnosis of OA were applied for eight subjects, which all got a positive reaction (late reaction in five subjects, dual reaction in three subjects). The mean level of GA observed during the challenge was 0.075 mg/m3 (range 0.065-0.084 mg/m3). In 16 workers (67%) serial PEF rate demonstrated a work-related effect. Levels of GA measured in the workplace were: short-term: mean 0.208 mg/m3, median 0.14 mg/m3, range 0.06-0.84 mg/m3; personal long-term: mean 0.071 mg/m3, median 0.07 mg/m3, range 0.003-0.28 mg/m3. In seven of the subjects (29%) specific IgE antibodies to GA were demonstrated. To conclude, the study indicated an immunological mechanism of GA. Both early and delayed reactions were demonstrated. Low airborne concentrations were measured at the workplaces where symptoms have occurred.

Pechter *et al*. (2005) reported on surveillance data from California, Massachusetts, Michigan, and New Jersey for 5 years (1993-1997). Among 305 healthcare workers with work-related asthma 8.9% (27 cases) was associated with exposure to GA. However, according to the authors this data cannot provide estimates of the true incidence and prevalence of work-related asthma as this condition is both under-diagnosed and under-reported by physicians.

McDonald *et al*. (2005) reported on the incidence of work-related asthma from the SWORD and OPRA projects in the UK, for which occupational physicians report, on a voluntary basis, new cases of OA. Annual averages reported for GA were: 31 cases (4%) during 1992-1995 and 15 cases (3%) between 1996 and 2001. In total, 213 cases were reported during this whole time-period, corresponding to 21 new cases per year. The authors reported an incidence of GA-induced OA cases of 3%. This calculated incidence, however, did not compare GA-exposed subjects without asthma with those having asthma, thus it may not show the true incidence. Furthermore, cases were reported on a voluntary basis.

Diar Bakerly *et al*. (2008) reported on trends in OA between 1991 and 2005 to the Midland Thoracic Society's Rare Respiratory Disease Registry Surveillance Scheme of Occupational Asthma (Shield) in the UK. A total of 1,461 OA cases were reported. GA was associated with 84 cases (6%). The annual incidence of OA was 42 per million of working population. Walters *et al*. (2013) reviewed asthma cases in the same database from 1991 to 2011. No notifications for GA were reported after 2005. According to authors the decline in notifications of OA for GA is consistent with increased awareness and reduction in use within the National Health Service (NHS) in the UK. Before the complete withdrawal of GA, i.e., before 2005, GA was instead the most frequently implicated agent with 69 cases out of 182 reported from 1991 to 2011 (corresponding to 38%).

Copeland and Nugent (2015) reported on a case of a 55-year-old woman referred for evaluation for chronic cough. The patient had no health problems until one year prior to her presentation to the clinic. She complained of chronic, persistent, non-productive cough and episodic shortness of breath. The woman had previously been employed at an endoscopy lab where she was routinely exposed to a 2.5% GA solution throughout her employment. The lab did not have special ventilation or hoods, and she did not wear a respirator. The woman worked in this lab for approximately one year, but she was forced to quit work due to respiratory symptoms (Copeland and Nugent, 2015).

Several studies reported asthma cases in relation to cleaning agents containing GA. Respiratory diagnoses attributed to cleaning agents were extracted from the Health and Occupation Research surveillance network, 1989–2017. Incidence, trends in incidence and incidence rate ratios by occupation were investigated. A total of 779 respiratory cases were attributed to cleaning agents. Diagnoses were predominantly asthma (58%) and inhalation accidents (27%) with frequently reported chemical categories being aldehydes (30%) and chlorine/its releasers (26%). For GA alone, 172 cases of OA were reported. However, the last case report for GA was from 2006, reflecting the results of banning GA in UK's health care sector (Carder *et al*. 2019).

Asthmatic reactions during specific inhalation challenges (SICs) in workers with cleaning-related asthma symptoms were studied in a retrospective case series analysis. Cases included were all participants with work-related asthma who completed an SIC procedure with the cleaning/ disinfection products suspected of causing work-related asthma over the period 1992–2011 in a tertiary centre hospital in Belgium. Challenge exposure to the suspected cleaning agents elicited a ≥ 20% fall in FEV1 in 17 (39%) participants. GA induced a positive SIC in 4 patients (1 case in combination with quaternary ammonium compounds) (Vandenplas *et al*. 2013).

Li and co-workers (2018) reported on 22 cases of work-related asthma among patients referred to an asthma and airway centre in Canada from 2000 to 2014. Of those, 12 were diagnosed with OA and 10 with work-exacerbated asthma (WEA). Specific causative chemical agents were usually not confirmed; however, two OA-cases and two WEA-cases had been exposed to GA during their work.

Takigawa and Endo (2006) summarised the health effects caused by GA. The authors list numerous cases of OA (in nurses, respiratory technologist, laboratory technicians, x-ray secretary, radiographers, etc.).

The American Association of Occupational and Environmental Clinics developed specific evaluation criteria used to review whether substances are sensitising agents or irritants (Rosenman and Beckett, 2015). Experts confirmed that GA fulfils both major criteria and 3 of 4 minor criteria for sensitiser induced asthma and thus meets the criteria of being an occupational asthmagen.

In the report of the Agency for Toxic Substances and Disease Registry (ATSDR, 2017) a study from Teta *et al*. (1995) is summarised (full study was not assessed by the dossier submitter). No indications of GA-induced respiratory sensitisation were observed within a group of 218 workers employed at a GA production facility. The period of assessment was 1959–1992. The average time spent in the GA production or drumming areas was 3.8 years and workplace time-weighted average (TWA) GA concentrations between 1977 and 1992 ranged from 0.16 to 0.33 mg/m3, except for 1982 when the TWA was 4.2 mg/m3 (ATSDR, 2017).

Vyas *et al*. (2000) conducted a cross-sectional study on staff from endoscopy units in the UK. A total of 466 current workers and 68 ex-workers were approached. Of the 68 ex-employees that had left work within the past 5 years, 26 (38.2%) had done so for health reasons. Of those 26 ex-nurses, 18 were included in the study along with 348 current nurses, from in total 59 endoscopy units. Thus, all ex-employees included in the study had been exposed to GA and had left work for health reasons (including symptoms of the skin and upper and lower respiratory tract). 318 current workers had been exposed to GA and 30 workers had been exposed to succinaldehyde-formaldehyde. Ten ex-employees with work related symptoms of the lower respiratory tract when employed on the endoscopy units, continued to have one or more symptoms of the lower respiratory tract despite no longer being in direct contact with GA (one had continued exposure), two other ex-employees left due to work related symptoms of the nose, and two cases due to work related symptoms of the eyes and nose. Six ex-employees recorded persistent eye or nasal irritation, five of whom had no continuing exposure to GA. Contact dermatitis was the most often reported work-related symptom, followed by nasal and eye irritation. Ten of 12 ex-employees with symptoms of the lower respiratory tract when employed in the endoscopy units continued to have such symptoms although no longer being

exposed to GA. Ten of the 12 ex-employees had a latency period of greater than 3 months (range 3 months to 7 years) before the start of lower respiratory tract symptoms. Three had latency periods of 3 years or more. Six of 12 with lower respiratory tract recorded symptoms occurred only on workday evenings or nights. Lung function analysis using spirometry showed a significantly lower lung function in the ex-employees compared with current workers (although ex-employees were few). An analysis showed no difference in lung function between smokers (n=104) and non-smokers (n=197). PEF rate was measured for 17 of the current workers that reported lower respiratory tract symptoms. According to the authors no cases of bronchial asthma (>10% diurnal variation in PEF rate recordings) were found. Immunological tests identified only one current worker with positive IgE specific to GA. This specific worker had symptoms in the eyes and nose, but not in the lower respiratory tract. In addition, airborne concentrations of GA at the workplaces were measured. Geometric mean peak GA level (in 43 units with a total of 267 nurses) was 0.06 (range <0.001–1.08) mg/m3 and geometric mean background GA level (in 52 units with 308 nurses) was 0.01 (range 0.002–0.1) mg/m3. Only for chronic bronchitis was exposure to GA significantly associated with an increased risk of symptoms. At least two comments to this study were published as response to the authors, of which one questioned the lack of asthma cases in the study by Vyas *et al*. (2000). The authors of the comment consider, based on the peak flow records for three subjects (current workers), as reported in the study by Vyas *et al*. 2000, might indeed indicate OA, hence suggesting that 3 of 17 current workers that were tested (18%) may have had asthma (response to Vyas *et al*. 2000 by Anees *et al*. 2001).

4.1.2.3 Acute respiratory effects

There are a few case reports on acute effects of GA exposure related to respiratory symptoms, respiratory distress, and subsequent deaths. As described in the ATSDR report on GA (2017), a 78-year-old male, who deliberately ingested an unspecified quantity of a biocide containing GA and a quaternary ammonium compound, developed acute respiratory distress and severe metabolic acidosis, and subsequently died; the respiratory distress was likely secondary to metabolic acidosis.

Another report involves a 19-year-old female that deliberately ingested an unspecified quantity of a biocide containing 15% GA and 10% coco benzyl dimethyl ammonium chloride (Perera et al. 2008). This subject developed acute respiratory distress and severe metabolic acidosis, but subsequently recovered.

Thumtecho *et al*. (2020) describes the clinical characteristics, outcomes, and factors associated with death of cases poisoned by GA-containing products in a 5-year retrospective cohort study (2013-2018) using data from the Ramathibodi Poison Center. Most cases were accidental through the oral route of exposure, while 6 patients were exposed by inhalation. Local effects were common. Systemic signs and symptoms occurred in 149 patients (61.1%) and included abnormal vital signs, desaturation, altered mental status, hypo/hypernatremia, hypokalemia, low bicarbonate/metabolic acidosis, acute kidney injury, hepatitis, and rhabdomyolysis. Most cases were fully recovered, the mortality rate was 3.7%. Of a total of 244 cases, 46 patients developed respiratory symptoms. In total, 9 patients died, of which 5 presented respiratory symptoms. Respiratory symptoms were among the factors that differed statistically between deceased and surviving patients (other factors included GA amount, neurological symptoms, and acute kidney injury). After using a multivariate analysis, however, respiratory symptoms were no longer statistically significantly associated with death. GA-containing products were mainly used as farm disinfectants with a median concentration on 15%. Most products (76%) also contained co-formulants, such as formaldehyde.

The involvement of a sensitising mechanism in these cases is not known.

4.2 Summary and discussion of human health hazard assessment

GA is a respiratory and skin sensitiser with a harmonised classification as Resp. Sens. 1. and Skin Sens. 1A according to CLP.

There are numerous well-documented cases of OA caused by GA exposure reported in the scientific literature. Several studies describe both an early onset and a late phase asthmatic reaction. Spirometry has demonstrated permanent effects on lung function in ex-employees exposed to GA, and first symptoms appeared between 3 months and 23 years after the exposure started.

Several studies reported an increase of IgE antibodies specific to GA both in humans and mice following exposure to the substance. The amount of GA-specific IgE antibodies has also shown to increase after dermal exposure with increased dose in experiments with mice.

Rosenman and Beckett concluded in their study from 2015 that GA is an asthmagen, based on specific evaluation criteria for respiratory sensitisation. They arrived at this conclusion based on 44 clear cases of OA, reported in 7 scientific peer-reviewed articles. As described in this document, additional cases have also been found in the literature (see section 4.1.2). The majority of studies include health care workers and nurses, but there are also reports of GA-induced asthma in, for example, workers in x-ray departments, radiologists and cleaners.

Conclusion

Based on findings in humans, it is beyond doubt that GA is a respiratory sensitiser. In addition, GA has a harmonised classification according to the CLP regulation for respiratory sensitisation. Moreover, animal and human data clearly demonstrate that the substance is a skin sensitiser. GA also has a harmonised classification for skin sensitisation.

5. Environmental hazard assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57(f) of the REACH regulation.

6. Conclusions on the SVHC Properties

6.1 CMR assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57(f) of the REACH regulation.

6.2 PBT and vPvB assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57(f) of the REACH regulation.

6.3 Assessment under Article 57(f)

6.3.1 Summary of the data on the hazardous properties

Glutaraldehyde is covered by index number 605-022-00-X of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3, classified amongst other hazards as a respiratory and skin sensitiser in category 1 and 1A, respectively.

6.3.2 Equivalent level of concern assessment

6.3.2.1 Human health

To determine whether the concern due to the respiratory sensitising properties of GA is of an equivalent level of concern to category 1A or 1B CMRs or PBT/vPvB substances, it has been assessed using the factors detailed in ECHA's general approach on the potential for a sensitiser to be identified as a substance of very high concern (SVHC) under the equivalent level of concern route of article 57(f) of the REACH Regulation[2]. The respiratory sensitising properties of GA have been examined with respect to each of these factors. In some cases, evidence on GA's skin sensitising properties is included as supporting information.

Type and severity of possible health effects

The severity of health effects due to exposure to respiratory sensitisers may range from mild symptoms such as wheezing, chest tightness, sneezing and cough, with immediate recovery when removed from the exposure to severe symptoms including significant asthmatic health effects that persist after exposure has ceased. Asthma may also have a lethal outcome.

Exposure to GA can cause asthma. A large body of evidence demonstrates the involvement of an immunologic response. The typical symptoms of GA-induced asthma are chest tightness, persistent cough, and wheezing (Copeland and Nugent, 2015; Di Stefano *et al*., 1999).

[2] https://www.echa.europa.eu/documents/10162/13657/svhc_art_57f_sensitisers_en.pdf/a50728cc-6514-486c-9108-193a88b4bc9e (accessed December 2020).

The following information regarding exposure to GA and the severity of the effects observed (i.e., sensitisation, chronic symptoms, and OA) is of relevance in determining whether the substance is of equivalent level of concern:

- Di Stefano and co-workers (1999) reported on 24 health-care workers with respiratory symptoms (cough, chest tightness, and wheezing) related to GA exposure, which improved on days away from work. Specific bronchial provocation tests for diagnosis of OA were applied for eight subjects, which all had a positive reaction. The mean level of GA exposure during the challenge was 0.075 mg/m3 (0.018 ppm). IgE antibodies specific to GA were demonstrated in seven of the subjects.

- Gannon *et al*. (1995) reported on seven workers from endoscopy or x-ray departments, exposed to GA that showed a pattern indicating OA after serial peak expiratory flow (PEF) measurements. Subjects were also exposed to low levels of GA during controlled specific bronchial challenge tests, which resulted in a 15% or more fall in FEV1. The subjects included had a history of asthmatic symptoms that improved when away from work. All seven workers tested in the study were diagnosed with OA.

- It has been reported that ex-employees with previous GA exposure had significantly lower lung function (measured by spirometry) than current employees, although no longer exposed to GA (Vyas *et al*. 2000). Asthma was not further studied in ex-employees; however, it was concluded that none of the current workers had asthma (PEF rate test). This conclusion was later questioned by other researchers, based on the choice of criteria for asthma diagnosis in the study. In their opinion, three of 17 current workers that were tested had symptoms indicating asthma. We consider that the study demonstrates that GA exposure can cause severe damage to lung function as well as it being permanent.

- A case study reports on a 55-year-old woman with persistent cough that had been exposed to GA for an extended period of time in her previous employment in a lab. The woman worked in the lab for approximately one year before developing respiratory symptoms and had to quit her employment. The authors concluded the women probably had OA, and symptoms persisted although the exposure to GA had ceased (Copeland and Nugent, 2015).

Potent allergens can induce sensitisation at very low doses, at short duration of exposure and/or infrequent exposure[3]. Even though the concentration required for induction is unknown, the available studies of GA-induced OA indicate low air levels also in workplaces where sensitisation have likely occurred.

Irreversibility of health effects

As described in section 4.1, respiratory sensitisation includes two phases. Induction of sensitisation means the irreversible priming of the immune system to recognise a foreign substance. Hence, induction leads to a prolonged and possibly lifelong increased risk of serious adverse health effects (asthma) and can be regarded as an adverse event. Elicitation occurs at re-exposure to the substance and gives rise to the manifestation of the allergy (i.e., the asthma). When exposure to the substance can be completely avoided, the elicitation phase is typically reversible, however prolonged exposure, for example in an occupational setting, may lead to chronic impairment of lung function, even when the exposure later is avoided.

[3] https://www.echa.europa.eu/documents/10162/13657/svhc_art_57f_sensitisers_en.pdf/a50728cc-6514-486c-9108-193a88b4bc9e (accessed December 2020).

With regard to GA-sensitisation, irreversibility of both induction and elicitation have been demonstrated. Gannon and co-workers (2006) reported on seven workers exposed to GA with asthmatic symptoms that improved when away from work. Moreover, Vyas *et al.* (2000) reported symptoms only on workday evenings or nights in six of 12 subjects with lower respiratory tract symptoms. These studies described symptoms of asthma that (re-)occured with exposure to GA and improve or vanish during periods with no exposure. This demonstrates that the induction of sensitisation to GA is a permanent impairment. Copeland and Nugent (2015) described a case where a woman with persistent cough was diagnosed with OA at least one year after the GA exposure had ended. Moreover, ex-employees with previous occupational GA exposure (had quit their employment within 5 years prior to the initiation of the study) were reported to have significantly lower lung function than current employees (Vyas *et al*. 2000). The two latter studies demonstrate that the symptoms of OA caused by GA may become irreversible.

Delay of health effects

Sensitisation is typically not an immediate effect and can take years to develop depending on the intensity, frequency and duration of exposure, the intrinsic properties of the allergen as well as the individual susceptibility. Since induction is an asymptomatic event, it is currently not known if the delay in health effect is due to a delay of induction, or a delay between the induction and the allergic reaction, or both. Moreover, since the clinical symptoms are used to diagnose the sensitisation, it is difficult to know if induction had occurred until an immune response is manifested. At that time, removal from, or reduction of the exposure, will not reverse the sensitisation. Studies describing a delay between exposure to GA and the onset of asthma are briefly summarised below.

The typical non-specific symptoms of GA induced OA (e.g., chest tightness and persistent cough) are generally coupled with a delay in symptoms after exposure and can thus lead to a delayed diagnosis (Copeland and Nugent 2015). A delayed diagnosis can lead to continued exposure to the substance, exacerbation of the symptoms and permanent impairment. A few such cases are described below.

- Vyas *et al*. (2000) reported permanent effects on lung function in ex-employees. Ten of the 12 ex-employees had a latency period ranging from 3 months to 7 years before the start of lower respiratory tract symptoms.

- Di Stefano *et al*. (1999) reported on 24 health-care workers that had respiratory symptoms (cough, chest tightness, and wheezing) related to GA exposure. All of them presented with a time interval between first exposure to GA and onset of respiratory symptoms (mean 6.7 years; range 1-20 years). In 10 of them (42%), the onset of cough, chest tightness, and wheezing was preceded by nasal symptoms (stuffiness, rhinorrhea, and sneezing) related to GA exposure for a variable interval of time (mean 5.3 years; range 6 months to 10 years).

- Gannon and co-workers (2006) reported on seven workers from endoscopy or x-ray departments, exposed to GA that showed a pattern indicating OA. The workers had been exposed to GA from 6 months to 23 years prior to onset of symptoms, which shows that there was a delay before the onset of the health effect.

- Copeland and Nugent (2015) reported on a woman seeking medical care after 1 year of unspecific symptoms including chronic persistent cough and episodic shortness of breath. The woman was no longer exposed to GA at the time of the evaluation, but the amount of time that had elapsed from her last GA exposure was not indicated in the study. The authors concluded that the distribution of inflammation and bronchial responsiveness can vary in a single patient with GA-induced OA, and therefore the evaluation may be more difficult than might be expected, and some patients will need multiple pulmonary function tests to characterise their airway disease.

Effects on quality of life

Permanent impairment of lung function, such as has been demonstrated for GA, may lead to a decreased quality of life and a requirement for long-term medication limiting the possibility of living a normal working and private life. Sensitised individuals may need to avoid all exposure to GA to avoid health issues which would mean the change of tasks, workplace, and profession. After prolonged exposure, an individual with OA may also react with asthma symptoms towards other non-specific irritants outside of the workplace and may eventually also lose the reversibility of symptoms when away from work (Quirce and Sastre, 2015).

The ethylenediamine (EDA) SVHC dossier[4] mentions a few studies that estimated the well-being of workers with asthma. For example, significantly increased mental stress, including depression and anxiety, were seen among subjects with asthma (Yacoub *et al*. 2007).

Knoeller *et al*. (2013) analysed data from the Behavioral Risk Factor Surveillance System Asthma Call-back Survey (2006-2009) for adults with current asthma who were or had been employed previously. An estimated 9.0% had work-related asthma. Individuals with work-related asthma were significantly more likely than those with non-work-related asthma to have poor self-rated health, impaired physical health, impaired mental health, and activity limitation.

Societal concern

As described above, health effects caused by GA may lead to permanent disability (Copeland and Nugent, 2015; Vyas *et al*., 2000), which can be regarded as a concern for society. A diagnosis of OA has major economic implications for the individual, their family, the state, and the employer. Most of the costs are borne by the individual/family and the state. There are direct and indirect costs for the state e.g., in terms of healthcare, retraining and unemployment support. For the individual, OA may lead to a decrease in salary by the need to change jobs, or unemployment. Production loss due to sick leave and reduced work capacity, costs for training of replacements and by introduction of additional exposure controls in the workplace may affect the employer (Ayres *et al*., 2011).

There are no data describing the cost attributed solely to GA-induced sensitisation. However, in the UK, the average cost per case of OA due to GA, latex, isocyanates or flour has been estimated to £130 000 – 135 000 (male) and £100 000 – 110 000 (female) (2004 prices) (Ayres *et al*. 2011). The total cost of all cases of latex and GA induced OA in the UK in 2003 was estimated between £3.6-3.9 million. This information can be used in combination with data on prevalence of respiratory sensitisation of workers to assess the economic impacts of GA induced OA. Useful information may also be brought forward by a survey currently performed by the OECD on the willingness-to-pay to avoid negative chemicals-related health effects (SWACHE), where asthma is one of the health effects considered[5].

Occupational asthma is a workplace hazard that is growing in prevalence every year. An incidence of approximately two to five cases of OA per 100,000 population each year, or about 15 to 20 percent of the overall adult-asthma burden has been reported (De Matteis *et al*., 2017). The incidence of OA induced by GA appears to range between 3-9% in the studies cited in section 4.1.2. This number may however not fully reflect the size of the problem since under-reporting and under-diagnosis are common for this type of health effect, as highlighted in the scientific literature.

There are additional costs associated with OA that cannot be directly translated into monetary terms. Such intangible costs come from various psycho-social consequences of dealing with a life-long disease. It has been shown that in patients who were matched for clinical and functional indices of asthma severity, individuals with OA are less satisfied with the quality of life even after

[4] MSC SVHC Support Document, Ethylenediamine, 2018: https://echa.europa.eu/documents/10162/f0a61fa4-64d1-2d19-35ed-d98134aec10d

[5] The costs and benefits of regulating chemicals - OECD

they were removed from the exposure, than in those with asthma unrelated to their work (Malo *et al*. 1993).

Is derivation of a 'safe concentration' possible?

The current mechanistic understanding of respiratory sensitisation makes it possible to assume that sensitisation is a threshold phenomenon. This entails that there will be levels of exposure below which induction/elicitation will fail to develop in most of the exposed individuals (taking differences in sensitivity into account). However, it is for a number of reasons difficult to establish a clear dose-response relationship for respiratory sensitisers necessary for the determination of such thresholds. There is a lack of regulatory accepted methods for risk assessment of respiratory sensitisers and typically also a lack of clinical/epidemiological data that would enable the identification of thresholds in humans. In addition, there are no accepted validated *in vitro* or animal tests available for respiratory sensitisation. Overall, it is difficult to derive reliable and protective exposure limits. Consequently, a qualitative risk assessment is typically recommended for this endpoint (ECHA, 2012)[6].

During the process of developing this document no data suitable for identifying thresholds for GA have been identified. The available data are limited to case reports and studies including few subjects and have not been designed for the purpose of dose-response determination. There is however evidence that GA sensitivity has been induced in workers, and that asthmatic responses were provoked by very low concentrations of GA (see for example Di Stefano *et al*., 1999).

Although OEL derivation approaches are well established for non-immunological endpoints based primarily on dose-response relationships, they are often less suitable for allergic reactions (Dotson *et al*., 2015). There are however national OELs set for GA.

Exposure Limits

The difficulty to derive a safe exposure level for GA is illustrated by (i) well-documented reports on cases of OA caused by GA where allergic reactions in the airways have been reported at low exposure levels and (ii) variable national and international occupational exposure limits (OEL) primarily based on respiratory effects. Asthma symptoms have frequently been reported after GA exposure at levels below 0.2 mg/m3 (0.05 ppm), which is the lowest national OEL reported in Europe (Table 4). For example, concentrations that triggered asthma in bronchial challenge tests ranged from 0.065-0.084 mg/m3 (Di Stefano *et al.* 1999) and 0.064-0.081 mg/m3 (Gannon *et al.* 1995).

Moreover, OELs for respiratory sensitisation are typically derived with the intention to protect workers from the induction of sensitisation. Since elicitation typically occurs at exposure levels lower than those required for induction, the OEL will not necessarily protect already sensitised individuals from the elicitation of asthma.

Europe

There is no EU-wide Indicative Occupational Exposure Limit Value (IOELV), or Binding Occupational Exposure Limit Value (BOEL) set for GA. However, several Member States have adopted eight hours limit values: Austria 0.4 mg/m3, Denmark 0.8 mg/m3, France 0.4 mg/m3, Poland 0.4 mg/m3 and Germany 0.2 mg/m3. Several Member States (Austria, Belgium Denmark, Finland, France, Germany, Ireland, Poland, Spain, and Sweden) have adopted short-term limit values ranging from 0.2 to 0.8 mg/m3. UK and Switzerland have a long-term OEL of 0.2 mg/m3[7].

The EU "Lowest Concentration of Interest" (EU-LCI) value (the lowest concentration above which, according to best professional judgement, the pollutant may have some effect on people

[6] Guidance on information requirements and chemical safety assessment, Chapter R.8 Characterisation of dose (concentration) response for human health, ECHA, 2012.
https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

[7] GESTIS database: GESTIS International Limit Values (dguv.de) (accessed on 18 December 2020).

in the indoor environment) for GA is as low as 1 µg/m3[8]. Although this value is derived from the critical effect of respiratory epithelium squamous metaplasia (based on a two-year inhalation mice study) the potential of GA as a respiratory sensitiser is emphasised in the background document and it is explicitly expressed that exposure of the general population to GA should be minimised and kept as low as possible.

Table 4: GESTIS summary of exposure limits for glutaraldehyde.

Substance	Glutaraldehyde			
CAS No.	111-30-8			
	Limit value - Eight hours		Limit value - Short term	
	ppm	mg/m³	ppm	mg/m³
Australia			0,1 (1)	0,41 (1)
Austria	0,1	0,4	0,1	0,4
Belgium			0,05 (1)(2)	0,21 (1)(2)
Canada - Ontario			0,5 (1)	
Canada - Québec			0,1 (1)	0,41 (1)
Denmark	0,2	0,8	0,2 (1)	0,8 (1)
Finland			0,1 (1)	0,42 (1)
France	0,1	0,4	0,2	0,8
Germany (AGS)	0,05	0,2	0,1 (1)	0,4 (1)
Germany (DFG)	0,05	0,21	0,1 (1)	0,42 (1)
			0,2 (2)	0,83 (2)
Ireland			0,05 (1)	0,2 (1)
Israel			0,05 (1)	0,21
Japan (JSOH)	0,03 (1)			
Latvia		5		
New Zealand			0,05 (1)	0,21 (1)
Poland		0,4		0,6
Singapore			0,2	0,82
South Korea			0,05 (1)	0,2 (1)
Spain			0,05	0,2
Sweden			0,1 (1)	0,4 (1)
Switzerland	0,05	0,21	0,1	0,42
USA - NIOSH			0,2 (1)	0,8 (1)
United Kingdom	0,05	0,2	0,05	0,2

	Remarks
Belgium	(1) Additional indication "M" means that irritation occurs when the exposure exceeds the limit value or there is a risk of acute poisoning. The work process must be designed in such a way that the exposure never exceeds the limit value. For evaluation, the sampled period should be as short as possible. However, the sampled period shall be long enough to perform a reliable measurement. The measured result shall be related to the considered period. (2) 15 minutes average value
Canada - Ontario	(1) Respirable aerosol
Canada - Québec	(1) Ceiling limit value
Denmark	(1) Ceiling limit value
Finland	(1) Ceiling limit value
Germany (AGS)	(1) 15 minutes average value
Germany (DFG)	(1) 15 minutes average value (2) Ceiling limit value
Ireland	(1) 15 minutes reference period
Israel	(1) Ceiling limit value
Japan (JSOH)	(1) Occupational exposure limit ceiling: Reference value to the maximal exposure concentration of the substance during a working day
New Zealand	(1) Ceiling limit value
South Korea	(1) Ceiling limit value
Spain	sen
Sweden	(1) 15 minutes average value
USA - NIOSH	(1) Ceiling limit value

US

[8] DocsRoom - European Commission (europa.eu) (accessed on 25 February, 2021).

The Agency for Toxic Substances and Disease Registry (ATSDR, 2017) indicates a minimal risk level (MRL) of 0.00003 ppm (0.0001 mg/m3) for intermediate-duration inhalation exposure. MRLs are substance-specific estimates that are intended to serve as screening levels (ATSDR, 2017). NIOSH recommends a ceiling limit of 0.2 ppm (0.82 mg/m3) that should not be exceeded at any time[9].

Additional Considerations

Skin exposure and sensitisation may be of importance for respiratory sensitisation, as respiratory sensitisation may be induced not only by inhalation but also by skin contact (ECHA 2017, Dotson *et al*., 2015). Hence, the strong skin sensitising property of GA is also of importance since it may result in heightened respiratory responsiveness following inhalation exposure.

GA for use in the health care sector has been substituted since 2002 in the UK because of health problems related to the substance, and thereafter the number of new GA-related asthma cases have decreased (Walters *et al*., 2013, 2018).

GA is identified as a candidate for substitution according to the Biocide Products Regulation (BPR), as it meets the criteria as a respiratory sensitiser (Article 10(1)(b) BPR). A candidate for substitution in the BPR means that the currently approved use as a biocide will be withdrawn when appropriate alternatives are available. This measure is in line with the requirements for substances included in Annex XIV of REACH. Thus, also for the coherence between EU regulations (i.e., that the property of respiratory sensitisation justifies substitution), candidate listing and inclusion in Annex XIV is considered suitable for this substance.

GA is mentioned as one substance that can cause onset of multiple chemical sensitivity, which has been reported among nurses handling GA (reviewed in Takigawa and Endo 2006; Ziem and McTamney, 1997). Symptoms associated with multiple chemical sensitivity are often unspecific and may include e.g., respiratory-, gastrointestinal-, neurologic- and immune-related symptoms. Patients appear to develop chronic illness, which may have a negative impact on their quality of life.

Cross-reactivity to formaldehyde in subjects with GA-induced asthma has been mentioned in several studies (Gannon *et al*., 1995, Shaffer and Belsito, 2000). Cross-reactivity may further impair the quality of life for GA-sensitised individuals. In addition, exposure to formaldehyde is relatively common also in non-working environments, as it is emitted from building materials, parquet flooring and carpets, household products, etc. (Vardoulakis *et al*., 2020).

Table 5: Summary of factors for ELoC assessment

Possible serious health effects?	Yes. GA is a respiratory sensitiser that can induce respiratory hypersensitivity, e.g., asthma, in exposed individuals. Asthma is a serious disease that can be life-threatening. With prolonged exposure, GA can also cause severe damage to lung function.
Irreversibility of health effects?	Yes. Sensitisation is an irreversible malfunction of the immune system which leads to a permanently increased risk of serious adverse health effects. It has also been shown that GA exposure can cause permanent damage to lung function.
Delay of health effects?	Yes. Latency periods of between 3 months and 23 years from the start of the exposure to GA to the onset of OA have been reported.
Quality of life impaired?	Yes. Impairment of lung function has been demonstrated long after termination of the exposure to GA. Such may lead to a requirement for long-term medication limiting the possibility of living a normal working and private life.
Societal concern?	Yes. There are costs for society in terms of e.g., healthcare, retraining, unemployment support, production loss (due to e.g., sick leave and reduced work capability) associated with GA-induced OA.
Is derivation of a safe	No. Such calculations are in general difficult to perform for respiratory sensitisers and no data suitable to calculate such limits have been identified for GA. The

[9] RTECS:MA2450000 - Glutaraldehyde - The Registry of Toxic Effects of Chemical Substances | CDC/NIOSH (accessed on 18 December 2020).

concentration possible?	difficulty to derive a safe concentration for GA can be illustrated by that the current OEL has been shown not to be fully protective for hypersensitivity of the airways.

6.3.3 Conclusion on the hazard properties and equivalent level of concern assessment

Glutaraldehyde is covered by index number 605-022-00-X of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3 (the list of harmonised classification and labelling of hazardous substances) and it is classified, amongst various other hazards, as a respiratory sensitiser (Resp. Sens. 1).

Glutaraldehyde is identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with respiratory sensitising properties for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 of the REACH regulation.

Evidence that the substance is of an equivalent level of concern includes:

Sensitisation is an irreversible malfunction of the immune system which leads to a permanently increased risk of serious adverse health effects. There are numerous studies on workers who became sensitised to GA and developed occupational asthma (OA). Asthma is a serious health effect that may result in permanent impairment of lung function. It has been reported that ex-employees with previous GA exposure have significantly lower lung function than current employees. Asthma may also have fatal effects.

Most studies on the effects of GA describe both an early onset (type I) and a late phase (delayed) asthmatic response. Several studies report an increase of IgE antibodies specific to GA both in humans and in mice after inhalation exposure to GA.

Symptoms of respiratory tract sensitivity have been shown to arise after variable periods of workplace exposure. Studies report symptoms appearing from 3 months up to 23 years from the first exposure to GA. In addition, the typical non-specific symptoms of GA-associated asthma (chest tightness, persistent cough, and wheezing) have been coupled with a delay in symptoms after exposure and may lead to a delayed diagnosis. If the symptoms cannot be immediately coupled to the exposure, there is a risk that exposure will continue and that the asthma will be further aggravated, leading to irreparable damage to lung function.

In addition to its respiratory sensitising properties, GA is a strong skin sensitiser with a harmonised classification as Skin Sens. category 1A. It has been indicated that skin exposure and skin sensitisation to GA may be of importance for respiratory sensitisation.

Long-term illness, such as asthma or impairment of lung function as a result thereof, limits the possibility of living a normal working and private life. Asthma may indeed require long-term medication. Sensitised individuals may need to change workplace and profession and retraining of affected staff may be required.

Several studies have investigated the cost implications of respiratory sensitisation for society in terms of e.g., healthcare, retraining, production losses (due to e.g., sick leave and reduced work capability) and impaired quality of life. There are also data on the economic or societal costs attributed to GA-induced OA that demonstrate large costs for the society.

There is currently no established method to determine a safe concentration for respiratory hypersensitivity, or data suitable to define such thresholds for GA. The difficulty to derive a safe

exposure level is illustrated by (i) well-documented reports on cases of OA caused by GA where allergic reactions in the airways have been reported at low exposure levels and (ii) variable national and international occupational exposure limits primarily based on respiratory effects.
Considering the type and severity of the health effects mentioned above, the delay and irreversibility of such effects, their impacts on the person's quality of life and the overall societal concern and costs, GA can be regarded as giving rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 of the REACH regulation.

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