Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report

Formaldehyde

Product-type 02
(Disinfectants and algaecides not intended for direct application to humans or animals)

November 2019

eCA: Germany

CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Procedure followed

This assessment report has been established as a result of the evaluation of the active substance Formaldehyde as product-type 02 (Disinfectants and algaecides not intended for direct application to humans or animals), carried out in the context of the work programme for the review of existing active substances provided for in Article 89 of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

Formaldehyde (CAS no. 50-00-0) was notified as an existing active substance, by B. Braun Melsungen AG and Lysoform – Dr. Hans Rosemann GmbH, hereafter referred to as the applicant, in product-type 2.

Commission Regulation (EC) No 1451/2007 of 4 December 2007[1] lays down the detailed rules for the evaluation of dossiers and for the decision-making process.

On 16 June 2009, the German Competent Authority received a dossier from the applicant. The eCA accepted the dossier as complete for the purpose of the evaluation on 15 December 2009.

On 29 June 2013, the eCA submitted to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Agency. Revisions agreed upon were presented at the Biocidal Products Committee and its Working Groups meetings and the competent authority report was amended accordingly.

1.2. Purpose of the assessment report

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of formaldehyde for product type 02, and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available from the Agency web-site shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data for that purpose has been granted to that applicant.

2. OVERALL SUMMARY AND CONCLUSIONS

2.1. Presentation of the Active Substance

2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis

Formaldehyde is a colourless gas with a melting point of -92°C which boils at -19,5°C (p = 1013 hPa). The vapour pressure of formaldehyde is 5490 hPa at 27°C, above aqueous solutions, the partial pressure (1% aqueous solution: 13 Pa; 25 °C) of formaldehyde is relatively low. Although formaldehyde is well soluble in water (up to 55%) and has a low volatilization potential from

[1] Commission Regulation (EC) No 1451/2007 of 4 December 2007 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. OJ L 325, 11.12.2007, p. 3

water. It is also soluble in alcohol and ether. Furthermore, the Henry Law constant is 0.034 Pa m^3/mol at 25°C and formaldehyde has a low logPow of 0.35.

The active substance is a colourless formaldehyde solution in water (25-55% formaldehyde. 0-7% methanol) with an irritating, pungent odour. For formalin a melting point of -15°C and a boiling point of 96°C could be found in the literature. For higher concentrated formaldehyde solutions the determination of the melting point is not possible, because formaldehyde polymerises at lower temperatures.

In aqueous solution formaldehyde exists as methylene glycol (HOCH2OH) and its oligomers, namely the low molecular mass poly(oxymethylene) glycols with the following structure HO(CH2O)nH (n = 1-8). Monomeric, physically dissolved formaldehyde is only present in low concentrations of up to 0.1 wt%. The density of the active substance (50% formaldehyde. 7% methanol) is 1.1346 g/cm^3 at 25°C and it is completely soluble in water and in all proportions soluble in toluene, ether, chloroform and ethylacetate. The vapour pressure of formalin is 187 Pa at 20°C, which is comparable with the vapour pressure of water.

A method for determining formaldehyde in aqueous solutions for industrial use is described in the international standard ISO 2227. The method as described is applicable to formaldehyde solutions with formaldehyde contents between 25% and 45%, but the field of application may be extended by modifying the mass of the test portion. The principle of the method is the reaction of formaldehyde with sodium sulphite, and acidimetric titration of the liberated sodium hydroxide using thymolphthalein as indicator.

Additionally derivatisation methods with following GC or HPLC detection are applicable for the determination of formaldehyde solutions

Acceptable primary methods are available for the determination of formaldehyde in air, drinking and surface water. Acceptable confirmatory methods were also presented for these matrices. No acceptable analytical method was presented for the determination of formaldehyde in soil. No relevant residues in food of plant and animal origin are expected to occur. Analytical methods for the determination of formaldehyde residues in food of plant and animal origin are not necessary.

Formaldehyde is classified as toxic. Therefore analytical methods for the determination of formaldehyde in body fluids and tissues are required. It is concluded from the study of Shara (1992) and from expert judgment that an exposure of formaldehyde has no influence on the formaldehyde concentration in body fluids or tissues. Thus, analytical methods in body fluids and tissues are not suitable for monitoring purposes. Nevertheless an analytical method (primary and confirmatory method) for the determination of formaldehyde in body fluids (urine) was provided. An additional method for the quantification of formaldehyde in water-based latex paints is provided. It could be useful for several formaldehyde releasers and for measurements in products.

2.1.2. Intended Uses and Efficacy

Formaldehyde has been evaluated for its use by professionals as a disinfectant in private and public health area.

The studies performed are sufficient at the Annex I inclusion stage. In the frame of product authorisation, further tests in the field of use have to be provided. Tests performed with the active substance show that formaldehyde has a bactericide and fungicide activity at a concentration of ≥ 0.5% within short term contact time (60min) and at concentration of 0.05% within long term contact time (24h). Further tests using formaldehyde show a sufficient disinfecting efficacy against viruses at concentrations between ≥ 0.064 and ≥ 0.92 after 120 min exposure. The proposed application rates of 0.05% - 12% of formaldehyde seem reasonable if formulated to a product.

Since the disinfecting action of formaldehyde is well established the data submitted was considered sufficient for the evaluation of the efficacy of the active substance at the Approval stage even though several shortcomings were identified in the studies: The information provided is only sufficient to show a basic efficacy of formaldehyde. This is accepted in the frame of Approval. Within the frame of product authorisation, essentially more information has to be provided: To support the claim bactericidal, fungicidal, virucidal and sporicidal further laboratory tests would be necessary. Additionally, further tests in the field of use have to be provided.

Mode of action:

Formaldehyde interacts with protein, DNA and RNA in vitro. The interaction with protein results from a combination with the primary amide and the amino groups. It reacts with carboxyl, sulfhydryl and hydroxyl groups. Furthermore, formaldehyde reacts with nucleic acid (e.g. DNA of bacteriophages or viruses). It inhibits viral DNA synthesis by forming DNA cross-links (e.g. in SV40) and can modify viral proteins (e.g. HBsAg and HBcAg of HBV). It penetrates bacterial spores and fungal conidia, acts sporostatic and inhibits germination.

In addition, in order to facilitate the work of Member States in granting or reviewing authorisations, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II.

2.1.3. Classification and Labelling

Classification and Labelling of Formaldehyde

Table 2-1 Proposed classification of formaldehyde based on Regulation (EC) No 1272/2008

	Classification	**Wording**
Hazard classes, Hazard categories	Acute Tox. 3* Acute Tox. 3* Acute Tox. 3* Skin Corr. 1B Skin Sens. 1 Muta. 2 Carc. 1B	Acute oral toxicity category 3 Acute dermal toxicity category 3 Acute inhalation toxicity category 3 Skin corrosion/irritation category 1B Skin sensitisation category 1A Mutagenicity category 2 Carcinogenicity category 1B
Hazard statements	H301 H311 H331 H314 H317 H341 H350	Toxic if swallowed Toxic in contact with skin Toxic if inhaled Causes severe skin burns and eye damage May cause an allergic skin reaction Suspected of causing genetic defects May cause cancer

Table 2-2 Proposed classification of formaldehyde based on Regulation (EC) No 1272/2008

	Classification	**Wording**
Hazard classes, Hazard categories	Acute Tox. 4 Acute Tox. 3 Acute Tox. 2 Skin Corr. 1B Skin Sens. 1A Muta. 2 Carc. 1B	Acute oral toxicity category 4 Acute dermal toxicity category 3 Acute inhalation toxicity category 2 Skin corrosion/irritation category 1B Skin sensitisation category 1A Mutagenicity category 2 Carcinogenicity category 1B
Hazard statements	H302 H311 H330 H314 H317 H341 H350	Harmful if swallowed Toxic in contact with skin Fatal if inhaled Causes severe skin burns and eye damage May cause an allergic skin reaction Suspected of causing genetic defects May cause cancer

Table 2-3 Proposed labelling of formaldehyde based on Regulation (EC) No 1272/2008

	Labelling	**Wording**
Pictograms	 GHS05  GHS06  GHS08	
Signal Word	Danger	Danger
Hazard statements	H302 H311 H330 H314 H317 H341 H350	Harmful if swallowed Toxic in contact with skin Fatal if inhaled Causes severe skin burns and eye damage May cause an allergic skin reaction Suspected of causing genetic defects May cause cancer
Suppl. Hazard statements	EUH071	Corrosive to the respiratory tract
Precautionary statements		

Summary and Conclusion:

The submitted data on acute toxicity require classification of formaldehyde in Acute oral toxicity Category 4 ("Harmful if swallowed", H302), based on an oral LD50 value of 640 mg/kg bw in rats; Acute dermal toxicity Category 3 ("Toxic in contact with skin", H311), based on a dermal LD50 of 270 mg/kg bw in rabbits; and Acute inhalation toxicity (gases) Category 2 ("Fatal if inhaled", H330), based on LC50 values of 1 mg/L x 0.5 h and 0.6 mg/L x 4 h in rats. Acc. to Regulation 1272/2008/EC, labelling as EUH071 "Corrosive to the respiratory tract" in addition to classification for inhalation toxicity is foreseen if the mechanism of toxicity is corrosivity. Considering that formaldehyde is a corrosive substance, additional labelling with EUH071 was regarded as appropriate.

Classification in Skin corrosion/irritation Category 1B ("Causes severe skin burns and eye damage", H314) and Skin sensitisation Category 1 ("May cause an allergic skin reaction", H317) is confirmed. However, based on EC3 values of 0.33- 0.96 % in various LLNAs, an induction rate of 100 % following intradermal injection at 0.25 % a.s. in the GPMT and a high frequency of occurrence in humans at relatively low exposure, formaldehyde should be subclassified into Skin Sens. Cat. 1A (strong sensitiser). Classification for respiratory sensitisation is not supported by current data. In principle, the database would require the following additional classification: Serious eye damage/eye irritation Category 1 ("Causes serious eye damage", H318) and Specific target organ toxicity – single exposure Category 3 ("May cause respiratory irritation", H335). However, both hazards are considered implicit when a substance is classified as corrosive, i.e. at $C \geq 25$ %.

The harmonised classification acc. to Reg. (EC) 1272/2008 includes the following concentration limits: Skin Corr. 1B, H314: $C \geq 25\%$; Skin Irrit. 2, H315: $5\% \leq C < 25\%$; Eye Irrit. 2, H319:

5% ≤ C < 25%; and STOT SE 3, H335: C ≥ 5%. Additional labelling with EUH208 ("Contains formaldehyde. May produce an allergic reaction.") applies at C ≥ 0.02 % (w/w).

There is strong evidence for genotoxicity/mutagenicity induced by formaldehyde in non-mammalian and mammalian cells in vitro and in vivo, namely DNA crosslinks, SCE, micronucleus formation as well as DNA adducts. Furthermore, there is supportive evidence for germ cell mutation from intra-peritoneal administered formaldehyde in male albino rats (Odeigah 1997) and male mice (SCE at 2, and 20 mg/kg x 5d; Tang; abstract). The Guidance to Reg (EC) No. 1272/2008 further notes: "classification as a Category 2 mutagen would generally apply if only intraperitoneal in vivo tests show mutagenicity/genotoxicity and the negative test results from the in vivo tests using other routes of application are plausible". Therefore, classification of formaldehyde in Mutagenicity Category 2 ("Suspected of causing genetic defects", H341) is confirmed.

A relationship between exposure to formaldehyde and haematopoetic malignancies, especially myeloid leukaemia, was indicated in epidemiological studies. Meta-analysis supported the association when taking into account the level of exposure to formaldehyde, in line with reports on lymphatic cell genotoxicity and bone marrow toxicity in highly exposed humans. Experimental evidence for a causal relation between an increased incidence of respiratory tract cancer following repeated formaldehyde inhalation is available from studies in more than one animal species, supported by mechanistic investigations. Therefore, classification of formaldehyde in Carcinogenicity Category 1B ("May cause cancer", H350) according to the criteria laid down in Regulation (EC) No 1272/2008 is confirmed.

Finally, methanol is present in the a.s. as impurity at concentrations of 0 - 7 % w/w. Currently, methanol is classified in Acute Toxicity Category 3 and Specific Target Organ Toxicity – Single Exposure (STOT SE): Category 1 with specific concentration limits of C ≥ 10% for STOT SE 1 (H370) and 3% ≤ C < 10% for STOT SE 2 (H371). At impurity levels above 3 % (i.e. in the range of 3-7 %), this would in principle trigger additional classification of the a.s. for STOT SE 2. However, as the concentration at which the impurity occurs is variable and classification for the a.s. formaldehyde is more severe and sufficiently protective, additional classification and labelling is not proposed.

Classification and Labelling of the biocidal product ("Dummy Product")

Table 2-4 Proposed classification of the biocidal product based on Regulation (EC) No 1272/2008

	Hazard classes, hazard categories, hazard statements	Wording
Classification	Acute Tox. 4, H302 Acute Tox. 3, H311 Acute Tox. 2, H330 Skin Corr. 1B, H314 STOT-SE 3, H335 Skin Sens. 1, H317 Muta. 2, H341 Carc. 1B, H350i	Harmful if swallowed Toxic in contact with skin Fatal if inhaled Causes severe skin burns and eye damage May cause respiratory irritation May cause an allergic skin reaction Suspected of causing genetic defects May cause cancer by inhalation

Remark:

No environmental classification is proposed.

Table 2-5 Proposed labelling of the biocidal product based on Regulation (EC) No 1272/2008

	Labelling	Wording

Hazard pictograms, signal words, hazard statements precautionary statements		Danger
	H302	Harmful if swallowed
	H311	Toxic in contact with skin
	H330	Fatal if inhaled
	H314	Causes severe skin burns and eye damage
	H335	May cause respiratory irritation
	H317	May cause an allergic skin reaction
	H341	Suspected of causing genetic defects
	H350	May cause cancer
	P271	Use only outdoors or in a well-ventilated area.
	P281	Use personal protective equipment as required.
	P301 + P330 + P331	IF SWALLOWED: rinse mouth. Do NOT induce vomiting.
	P303 + P361 + P353	IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower.
	P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minuts. Remove contact lenses, if present and easy to do. Continue rinsing.
	P308 + P313	IF exposed or concerned: Get medical advice/attention.
	P403 + P233	Store in a well-ventilated place. Keep container tightly closed.
	P405	Store locked up.

Summary & Conclusion:

The proposed classification and labelling of the biocidal product is inherited from the active substance.

No environmental classification is proposed for the active substance as well as the biocidal product.

2.2. Summary of the Risk Assessment

2.2.1. Human Health Risk Assessment

2.2.1.1. Hazard identification

Formaldehyde is of high chemical reactivity, causing local irritation or corrosion at exposed epithelia. There is also convincing evidence for skin sensitisation by the active substance. Formation of DNA-protein links is thought to lead to clastogenic effects. At concentrations causing cytotoxicity in the respiratory tract with induction of regenerative cell proliferation, formation of nasopharyngeal cancer has been established in rats.

2.2.1.2. Effects assessment

The industrial use of formaldehyde has a long history. Consequently, extensive research has been performed on the toxicology of formaldehyde and a wealth of human and animal toxicity data has been accumulated. Unfortunately, little of the available data has been acquired and reported in a way complying with current OECD and EU guidelines for the testing of chemicals.

Therefore, appropriate care needs to be taken in its interpretation. Nevertheless, it provides the information required for an assessment of the human health effects of formaldehyde.

Absorption, Distribution, Excretion, and Metabolism

In rats and mice, gastrointestinal absorption of ^{14}C-formaldehyde was reported to be rapid and virtually complete. Within 12 hours, 40 % of radioactivity was exhaled as CO_2, or excreted with urine (10 %) or, to a minor extent, with faeces (1 %) in rats. Total body ^{14}C-residues were 20 % after 24 hours and 10 % after 96 hours in mice.

After i. p. administration of a single dose ^{14}C-formaldehyde to male SD rats, 70 % of radioactivity was exhaled as CO_2 within 12 h, 5.5-9 % of radioactivity were found in urine.

The available data on dermal absorption indicate that formaldehyde is quantitatively absorbed from the skin surface. When absorbed from solution, the absorption process is obviously in direct competition with evaporation and systemic absorption may be delayed and/or limited by covalent binding at the site of application. Nevertheless, a significant fraction of the absorbed material or its (radioactive) metabolites enters the systemic circulation to be distributed widely and excreted with urine, faeces, and exhaled air. Taking this into account, a dermal absorption of 100 % formaldehyde is considered appropriate for risk assessment of its liquid formulations.

The default values of 75% and 25% for dilutions and concentrates according to EFSA Guidance on Dermal Absorption (2012) do not apply when experimental data suggests other values (CA-July13-Doc6.2.b – Final). Product/use specific information can be submitted for refinement at the product authorisation stage.

As a highly water soluble gas, inhaled formaldehyde readily passes over into the lining mucosa. Formaldehyde gas inhalation had no significant effect on the existing background levels in blood. This is indicative for rapid formaldehyde conversion at the site of entry resulting in metabolites and/or adducts that are apparently absorbed and distributed systemically. Thus, an inhalation absorption factor of 100 % is considered appropriate for risk assessment of formaldehyde gas

In rats, and mice, preferential absorption in the anterior regions of the nasal cavity was observed. Due to species-specific differences in anatomy and breathing pattern, larger fractions are predicted to be absorbed in the tracheobronchial region in man with more than 100-fold lower deposition in the pulmonary region.

Within animal tissues, formaldehyde reacts spontaneously and non-enzymatically with a range of sulfhydryl- and amino-compounds to form adducts, some of which can at least in part dissociate or decompose to release formaldehyde. Adducts with genomic DNA are sufficiently stable to react with proteins into cross-linked products.

Experimental evidence suggests that the spontaneous reaction with glutathione is the most important pathway for the detoxification of formaldehyde in animals and humans. This reaction is followed by enzymatic oxidation by alcohol dehydrogenase 5 (ADH5). Products of further hydrolysis are GSH and formate.

Following saturation of this pathway or in absence of glutathione, GSH-independent aldehyde dehydrogenase 1 (ALDH1, cytosolic) and 2 (ALDH2, mitochondrial) contribute significantly to oxidation of formaldehyde into formate.

Resulting formate can be excreted renally or following addition to tetrahydrofolate further consumed in one-carbon-transfer reactions or oxidised to form THF, CO_2 and NADPH.

As the major urinary metabolites in rats, adducts of formaldehyde with urea were identified in addition to formate.

Acute Toxicity

LD_{50} values in rats were between 640 and 800 mg/kg bw. Guinea pigs appeared more sensitive than rats, resulting in a LD_{50} value of 260 mg/kg bw.

Mortality after dermal administration occurred at similar doses as suggested by a dermal LD_{50} of 270 mg/kg bw in rabbits.

In rats, inhalation of formaldehyde resulted in LC_{50} values of 0.5 to 1.0 mg/L following exposure for 0.5 to 4 hrs. Exposure to 0.28 mg/L formaldehyde in air was associated with restlessness, excitation, laboured breathing, gasping and assumption of a lateral position in rats. Higher concentrations (0.6-1.7 mg/L) resulted in haemorrhage and oedema of the lung as well as oedema in liver and kidneys and hepatocyte necrosis.

Mortality following injection (s.c.) of formaldehyde was observed at similar doses compared to gavage administration with LD_{50} values of 420 and 300 mg/kg bw for rats and mice, respectively.

Irritation and Corrosivity

Studies on skin irritation performed to current testing guidelines are not available.

However, single and unoccluded administration of a concentration of 7-9 % formaldehyde in water was irritating in rat skin and a concentration of 15-18 % formaldehyde was reported to cause erosion in the skin of rats, mice and guinea pigs.

Previous risk assessments performed by OECD and WHO considered formaldehyde as skin irritant based on effects observed after administration of 0.1-20 % solutions to rabbit skin and a 1 % solution to guinea pig skin. In humans, single dermal application of 1 % formaldehyde in water (occluded) produced irritant responses in 5 % of individuals. Case reports of oral poisonings with 37-40 % formaldehyde solutions are in support of corrosive properties on mucosal tissues. Further dose-response data for skin irritation is available from repeated dose testing (see below).

Eye irritation studies in rabbits, rats and mice revealed corneal opacity following application of formaldehyde solutions with concentrations between 7 % and 15 % which was not reversible within the observation period. Therefore, formaldehyde should be regarded as “causing serious damage to eyes”. This is also in full agreement with the corrosive properties identified in skin irritation studies.

Exposure to formaldehyde in the air may cause local irritation of eyes, nose, throat and lung. In humans, irritation of the eyes was usually identified as the most sensitive endpoint. Pulmonary function was not affected. A NOAEC of 0.6 µg/L x 4 h (0.5 ppm) based on objective eye irritation and conjunctival redness in response to peaks of 1.2 µg/L is derived for risk assessment purposes. In addition, an experimental NOAEC of 0.36 µg/mL (0.3 ppm; acute) for subjective conjunctival (eye) irritation, and a population NOAEC of 0.12 µg/L (0.1 ppm) considering interindividual variability was suggested based on extensive review of the literature.

Skin sensitisation

Formaldehyde is a known skin sensitiser inducing Type IV allergic contact dermatitis. The sensitising properties of formaldehyde are confirmed by a large number of tests in laboratory animals, including guinea pig maximisation tests and local lymph node assays. In the local lymph node assays, EC_3 values between 0.33 % and 0.96 % formaldehyde in several vehicles were reported.

A substantial database on allergic skin reactions in humans is available from patch testing with the 1 % aqueous solution of formaldehyde. Incidences for existing sensitisation were 3 % (n=9986), 2.5 % (n=120) and 3.5 % (n=255) in dermatitis patients and 1.8 % (n=23564) in workers without contact dermatitis. In addition, dose-response data is available indicating a LOAEC for elicitation at 0.025 % (w/w) formaldehyde with a NOAEC (response rate ≤ 5 %) at 0.005 % (w/w).

However, the currently available methodology is not considered suitable for derivation of an acceptable exposure level protecting from sensitisation by formaldehyde which is relevant to human health. Nevertheless, the available data is in support of the current legal classification limit for formaldehyde formulations of ≥ 0.2 % (w/w) with regard to its sensitising properties and the resulting labelling provisions with EUH208 at ≥ 0.02 % (w/w).

Respiratory sensitisation

Regarding respiratory sensitisation, the majority of studies and reports in humans were not able to detect a relationship between asthma or allergic respiratory diseases and specific IgE antibodies against formaldehyde. This is supported by animal studies investigating IgE, IL-10 and IFN-gamma responses. Thus, the available data appear not to be sufficient to classify formaldehyde for respiratory sensitisation.

Short-term Toxicity

The submitted repeated dose studies generally suffer from a lack of guideline-conform reporting with respect to organs other than those that come into direct contact with formaldehyde in the process of substance administration, i.e. the stomach for oral and the respiratory tract for inhalation exposure. Such deficiencies severely constrain any independent evaluation of systemic toxicity of formaldehyde after repeated administration.

In rats, local effects after oral administration of paraformaldehyde via drinking water were observed in the forestomach (focal hyperkeratosis) and the glandular stomach (focal gastritis) and decreased plasma levels of albumin and total protein were seen at an exposure level of 125 mg/kg bw/day. The NOAEL for these effects was 25 mg/kg bw/day, but histopathology was not complete.

Two oral 90-day studies in rats and dogs reported reduced body weight gains from a dose level of approximately 100 mg/kg bw/d and suggested a NOAEL of approx. 50 mg/kg bw/d for both species. No local lesions were reported in the subchronic tests. An overall NOAEL of 15 mg/kg bw/d for local and systemic effects is derived from the limited subacute and subchronic, and a full chronic study in rats. This value also covers the effects reported from the 90-day dog study.

Data on toxicity after repeated dermal exposure to formaldehyde-containing solutions is limited. A NOAEC of 0.1 % has been previously derived based on reversible skin irritation following 3 weeks administration of 0.5 % formaldehyde in female mice with local observation of the application site.

Local effects on the epithelia of the respiratory tract were the main findings in rats, mice and cynomolgus monkeys after inhalation exposure to formaldehyde gas. The type of the lesions, squamous metaplasia and hyperplasia, was identical in all three species, indicating comparability of the mechanisms involved. Hamsters and mice appeared to be less sensitive.

In rats, at sufficiently high concentrations (≥ 12 µg/L), a single exposure for 6 hours resulted in vacuolar degeneration, cell necrosis, exfoliation and multifocal erosions of the nasal epithelium. These lesions progressed with repeated exposure, with ulcerations and inflammatory cell infiltrates being evident after 4 days and epithelial hyperplasia and metaplasia developing by day 9. A short-term NOAEC of 2.4 µg/L for local effects on the nasal epithelium may be derived from the study in rats treated for up to 42 days. A medium-term NOAEC of 1.2 µg/L is suggested by the results of 6-mo studies in rats and monkeys. Taking into account the dose-response after chronic inhalation exposure (LOAEC 2.4 - 7.2 µg/L), it is reasonable to conclude that the threshold dose for local lesions remains practically constant with increasing time, while the nature of the lesions reflects the progressing pathology. Hence, an overall (short/medium/long-term) inhalation NOAEC of 1.2 µg/L for local effects based on the 6-mo study in rats and monkeys is proposed.

There is evidence that inhalation exposure to formaldehyde concentrations exceeding the threshold for local inhalation toxicity may potentially be associated with systemic effects: changes in clinical chemistry parameters were indicative for possible adverse liver changes in male rats.

Inhalation exposure of rats over 2 weeks caused a dose-dependent increase in plasma lipoxygenase, plasma protein carbonyls, plasma and liver lipid peroxidation as well as lymphocyte and liver cell DNA damage along with indications for an ongoing inflammatory response. Other inhalation studies indicated adverse effects on the male reproductive system at exposure concentrations of 10 and 6 µg/L at the level of testis histopathology and serum testosterone, respectively. It is, however, unclear if the systemic effects discussed above are primary, i.e. directly resulting from formaldehyde or its metabolites, or secondary to local lesions and inflammatory reactions. This uncertainty is reflected by derivation of a systemic reference dose to protect from potential internal effects following prolonged exposure to low concentrations of the active substance.

Genotoxicity

***In vitro* tests:**

Formaldehyde revealed mutagenic and clastogenic activity *in vitro* in bacterial and mammalian cell systems, including the Ames test, TK and HPRT tests, sister chromatid exchange assays, chromosomal aberration and micronucleus tests without metabolic activation.
Formaldehyde is known to induce single strand breaks and DNA-protein crosslinks (DPX) resp. DNA-DNA crosslinks which can cause base pair substitutions and deletions.
For DPX, time- and concentration-dependent repair of the lesions *in vitro* was reported.

***In vivo* tests:**

Local genotoxic effects at the site of first contact

Following gavage administration of formaldehyde, increases in micronuclei and other nuclear abnormalities in the epithelial cells of the stomach, but also in duodenum, ileum and colon in rats were observed.

After inhalation exposure to formaldehyde gas, the formation of DNA-protein cross-links (DPX) in the nasal epithelium has been demonstrated in rats and monkeys, as well as in the trachea, larynx and major airways of monkeys. In rats, at higher concentrations a steep dose-response relationship for DPX formation within the nasal mucosa suggests saturation of detoxification and/or repair mechanisms.

After repeated inhalation exposure of rats to formaldehyde an increase in chromosomal aberrations was reported in alveolar macrophages. In humans, there is evidence for clastogenicity in the nasal epithelium and in buccal cells after repeated exposure to formaldehyde.

Overall, there is convincing evidence, that formaldehyde exposure can induce local genotoxic effects at the site of contact.

Systemic genotoxicity:

Standard cytogenetic, micronucleus and comet assays failed to show systemic effects in samples of bone marrow or peripheral blood after inhalation exposure of rats and oral administration of formaldehyde in aqueous solution to mice.

Following i.p. injection of formaldehyde, a dose-dependent increase of sperm head abnormalities and genotoxic effects in germ cells were observed in rats and mice, respectively. It was noted that the relevance of this route is limited to hazard identification. Moreover, some older studies demonstrated mutations in *Drosophila melanogaster* germ cells.

Investigations on exposed human subjects resulted in negative, inconclusive or positive findings. An increase in the number of micronuclei and chromosomal aberrations in peripheral lymphocytes were reported following inhalation exposure to formaldehyde over 12 wks. Further studies assessing chromosomal aberrations, micronuclei and sister chromatid exchange in peripheral lymphocytes of exposed human subjects were extensively reviewed in 2006. For each of these endpoints, approximately balanced numbers of reliable studies indicating presence and absence of systemic genotoxicity were found.

A recent study revealed a possible influence of formaldehyde exposure on haematopoietic functions: a pancytopenic effect in exposed workers as well as a decrease in colony formation from progenitor cells in formaldehyde-exposed workers compared to workers in a non-exposed control group as well as increases in monosomy of chromosome 7 and trisomy of chromosome 8 - typical genetic aberrations for acute myeloic leukaemia (AML) - were observed in cultivated cells (*ex vivo)*.

Chronic Toxicity / Carcinogenicity

Currently, there is no evidence for carcinogenicity of formaldehyde when administered via the oral route. In an acceptable study with exposure of rats through drinking water, local effects in the forestomach (focal papillary epithelial hyperplasia, hyperkeratosis, ulceration) and the glandular stomach (atrophic gastritis, focal ulceration, glandular hyperplasia) and renal papillary necrosis was evident with a long-term oral NOAEL of 15 mg/kg bw/d (0.026 % in drinking water). No other tissues appeared to be affected and no treatment related tumours were reported.

Reconsidering the NOAEL of 25 mg/kg bw/d from the 28-d oral rat study and the effects observed at 125 mg/kg bw/d, it seems reasonable to assume that the threshold dose for local lesions remains practically constant with time, while the nature of the lesions reflects the progressing pathology. Hence, it is proposed to use the long-term NOAEL of 15 mg/kg bw/d as an overall value for subacute, subchronic and chronic oral exposure.

Preliminary data are available for the chronic exposure via the dermal route. In a mouse study over 60 weeks, concentrations of 1 and 10 % formaldehyde induced a slight hyperplasia of the epidermis and possibly some small skin ulcers at the higher dose level. No treatment-related tumours were detected in the skin or any other organ. However, the number of animals is insufficient to exclude a risk with an acceptable level of certainty. In another study, an initial dose of 50 µl of a 10 % formaldehyde solution was administered to the skin followed by thrice weekly applications of 100 µL 0.1, 0.5, or 1 % solution for 26 weeks in mice. No skin tumour formation but minimal local irritation of the skin was reported at concentrations of 0.5 and 1 %, but not at 0.1 %. This database is not found suitable to derive a long-term dermal NOAEC for formaldehyde.

Long-term inhalation exposure to formaldehyde induced local effects, ranging from inflammatory processes to mainly squamous cell carcinoma in the nasal cavity of male and female rats. Squamous cell carcinoma formation in the nasal epithelia became notable after 18-19 months of exposure to 12 µg/L and after approx. 12 months of exposure to 18 µg/L. The lowest concentration at which squamous cell carcinoma formation was observed was 7.2 µg/L.

In mice, squamous cell carcinoma was observed in animals exposed for 24 months to 18 µg/L formaldehyde. Lifetime exposure of hamsters to 12 µg/L formaldehyde in air for 5 h/d and 5 d/wk caused nasal epithelial metaplasia and hyperplasia in a small but significant number of animals.

In conclusion, experimental evidence in rats and mice demonstrates that long-term formaldehyde gas inhalation causes tumours in the upper respiratory tract from exposure concentrations of 7.2 µg/L.

Taking into account the dose-response for non-neoplastic lesions after subacute, subchronic and chronic inhalation exposure, it can further be concluded that the threshold dose for local lesions remains practically constant with increasing time, while the nature of the lesions reflects the progressing pathology. Hence, an overall inhalation NOAEC of 1.2 µg/L for local effects based on the 6-mo studies in rats and monkeys is derived.

Reproduction Toxicity

Developmental Toxicity:

Data in rats and mice do not indicate a teratogenic potential of formaldehyde after systemic exposure. Maternal toxicity, manifesting as body weight loss, was observed in rats following inhalation exposure to 47 µg/L x 6 h/d. Embryofoetal toxicity was present at the same dose and resulted in decreased foetal weight and reduced or delayed ossification of thoracic vertebrae and sternal bodies.

A gavage study in pregnant mice provided evidence of severe maternal and slight embryo-foetal toxicity at a dose of 185 mg/kg bw/d. No relevant effects on the dam or the foetus were observed at the dose level of 148 mg/kg bw/d. Overall, there is no concern for developmental toxicity of formaldehyde.

Reproduction Toxicity:

No fertility studies performed in animals according to relevant OECD or EC guidelines have been submitted and the epidemiological data on reproductive effects in exposed humans are inconclusive.

Inhalation studies revealed effects on the male reproductive system including reduced testosterone production, reduced spermatogenesis, impaired sperm function and reduced GSH levels as well as increased rates of sperm abnormalities and elevated malonedialdehyde concentrations following exposure to ≥ 6 or 10 µg/L, indicating that the testis may be a target tissue for formaldehyde toxicity. Unfortunately, a NOAEC was not determined and animals have not been mated to assess effects on fertility.

Overall, the observations (and the absence of corresponding alerts within the human data) support the general presumption that effects on male reproductive functions may be relevant for inhalation exposure only at higher concentrations concurrent with other local and/or systemic toxicity.

Neurotoxicity

No evidence of neurotoxicity was reported in the repeated dose toxicity studies. However, studies conducted to assess specific behavioural consequences of formaldehyde inhalation in rats measured an acute decrease of exploratory behaviour and showed impairment of learning ability in a water maze test. Overall, the effects observed are considered to be related to an unspecific irritation of the nasal/olfactory mucosa and their relevance to human health remains unlikely.

Medical Data

Epidemiologic studies in humans have produced convincing evidence that formaldehyde has a carcinogenic potential in humans. Associations between inhalation exposure to formaldehyde and an increase in standardised mortality ratios (SMR) and/or relative risk (RR) were found for cancers of both, the upper respiratory tract (nasopharyngeal cancer) and the lymphatic system (especially myeloid leukaemia) in large cohort studies, respectively.

Cancers of the upper respiratory tract

In a cohort study, an increased incidence of nasopharyngeal cancer (NPC) was positively associated with exposure metrics (average intensity, peak exposure) that specify a high concentration of formaldehyde at the sensitive sites. An almost 2-fold excess of deaths due to nasopharyngeal cancer was observed in workers with high peak exposure as compared to the group of non-exposed workers and a 4-fold excess was observed for high cumulative exposure as compared to low-exposed groups working at the same production plant. The increases in RR did not gain statistical significance. However, trend tests for both exposure metrics were significantly positive indicating that tumour-related deaths were dose-related. Furthermore, the RR for selected upper respiratory tract tumours (6 tumour types including nasopharyngeal cancer) was significantly increased when an average intensity concentration of 1.2 µg/L (1 ppm) was exceeded.

In various case-control studies inconsistent results have been found. Some of them failed to show significant effects, whereas others and meta-analysis revealed significant increases in risks for cancer in the nasopharyngeal region.

Nevertheless, there is sufficient evidence to assume a causal relationship between formaldehyde exposure and induction of nasopharyngeal cancer in humans: Rodents and non-human primates show dose related cytotoxic-proliferative and metaplastic lesions with an anterior to posterior gradient and with species-specific distribution in rats and monkeys. In the most affected area, squamous cell carcinoma was induced in rats. Considering the upper respiratory tract epithelium as the target tissue, along with the physiological and anatomical differences between rodents and humans (e.g. breathing pattern and morphology of the upper respiratory tract), recent results from cohort-studies showing enhanced mortality rates of nasopharyngeal cancer in formaldehyde exposed workers are in line with the experimental data in rats. It is therefore proposed to classify air-borne formaldehyde as a human carcinogen.

Haematopoietic cancers
The results of recently published cohort studies support an association between both, high peak exposure as well as extended periods of formaldehyde exposure and neoplasms of the haematopoietic system. Other cohort studies and case control studies, however, failed to show such associations. Although the data base on *in vivo* genotoxicity studies on lymphocytes and progenitor cells was considered currently inconclusive, positive findings were typically reported in highly exposed humans and potential mechanisms for such effects were postulated.

Summary & Conclusion:

Thresholds for carcinogenic effects

Regarding the carcinogenicity in the upper respiratory tract, the epidemiological data as well as the dose-response curve in animal carcinogenicity studies and previous dose-response modelling exercises clearly support the existence of a practical threshold.

According to the current understanding, a risk for potential induction of haematopoietic cancers by formaldehyde may be regarded unlikely in humans and animals at doses that do not saturate local detoxification at the site of first contact. This conclusion is confirmed by an assessment of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and Environment which concluded that formaldehyde should be treated as genotoxic carcinogen with a practical threshold, allowing for derivation of reference values. This is supported by results from long-term studies in rats after inhalation exposure which provide no firm indications that formaldehyde is able to induce neoplasms of the haemotopoietic system in animals.

It should however be mentioned that in 2012 RAC concluded that there is no clear threshold for the identified key events cell proliferation and primary DNA damage (DPX):" Overall there are indications of a threshold at 2 ppm (LOAEC) for cell proliferation (as indicated from hyperplastic/metaplastic/dysplastic precursor lesions and increased cell proliferation activity) and DPX formation, and this LOAEC can be considered to point to `practical threshold´ for the effects. However, data also indicate non-significant dose-related increases in cell proliferative activity and DPX formation below 2 ppm. Taking into account the overall limited database below 2ppm, no firm conclusion on the presence of a biologically meaningful threshold, the existence of linearity of dose-response curve in the low dose range (< 2ppm) for both effects can be made." (RAC Opinion proposing harmonised classification and labelling at EU level of Formaldehyde, CLH-O-0000003155-80-01/F. Adopted 30 November 2012, ECHA).

Derivation of Reference Values

The overall NOAEL of 15 mg/kg bw/d for subacute, subchronic and chronic oral exposure based on stomach lesions, renal papillary necrosis and reduced body weight gain observed in rats following exposure to ≥ 82 mg/kg bw/d in the drinking water provides the relevant starting point for derivation of oral and systemic reference doses. By setting a default assessment factor (AF) of 100 and taking into account an oral absorption of 100 %, identical values for systemic exposure to formaldehyde are proposed. ADI and ARfD are not considered necessary based on the 2014 evaluation of the EFSA FEEDAP Panel (SCIENTIFIC REPORT OF EFSA, Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sources. EFSA Journal 2014;12(2):3550). It concluded that the relative contribution of exogenous formaldehyde from consumption of animal products (milk, meat) from target animals exposed to formaldehyde-treated feed was negligible compared with formaldehyde turnover and the background levels of formaldehyde from food sources

Acute Acceptable Exposure Level (AEL_{acute}) = 0.15 mg/kg bw/d

Medium-term Acceptable Exposure Level ($AEL_{medium-term}$) = 0.15 mg/kg bw/d

Long-term Acceptable Exposure Level ($AEL_{long-term}$) = 0.15 mg/kg bw/d

Due to the high reactivity of formaldehyde, local effects dominate the toxicity profile of the substance. Ocular (conjunctival) and nose/throat irritation were reported in humans at concentrations around 1 µg/L formaldehyde in the air. Lesions of the nasal epithelium were observed in rats at slightly higher exposure concentrations that correspond to inhaled doses of 1.8-3 mg/kg bw/d. This is considerably lower than the oral NOAEL forming the basis for the Systemic Reference Dose (see above). Therefore, additional external Acute Exposure Concentrations are derived for inhalation exposure.

The most sensitive endpoint in humans exposed by inhalation is subjective conjunctival (eye) irritation, for which an experimental NOAEC of 0.36 µg/L (acute) and a population based NOAEC of 0.12 µg/L (acute-chronic) have been concluded. An assessment factor of 3 accounting for intraspecies toxicodynamic variability would be used to derive an AEC of 0.12 µg/L from the recent acute study in human volunteers. This value is supported by the identical population based NOAEC concluded from an extensive evaluation of a collection of studies on workers, volunteers and exposed population.

In addition, the overall NOAEC of 1.2 µg/L based on degenerative and pre-neoplastic lesions of the nasal mucosa observed in rats and monkeys following subchronic exposure to formaldehyde gas concentrations of ≥ 3.6 µg/L for 22 h/day, as well as equivalent changes observed in rats following subacute or chronic exposure to similar formaldehyde concentrations provides another relevant starting point for the derivation of inhalation reference concentrations. The evaluated data including regulatory reviews support the view that humans are not more sensitive to local inhalation toxicity of formaldehyde than rats, allowing for reduction of the AF for interspecies extrapolation to 1.

Comparison of effect levels from studies of different duration suggest that the threshold levels remain constant, while the nature of the observed lesions may reflect a progressing pathology.

Therefore, identical **Acceptable Exposure Concentrations** are proposed for **acute**, **medium-term** and **long-term inhalation exposure**:

$AEC_{acute\ inhalation}$ = 0.12 µg/L air

$AEC_{medium-term\ inhalation}$ = 0.12 µg/L air

$AEC_{long-term\ inhalation}$ = 0.12 µg/L air

based on combined human and animal data.

This value provides a MoE of 20 between the proposed AEC and the NOAEC of 2.4 µg/L for carcinogenic effects in the upper respiratory tract observed in rats and mice at exposure concentrations not lower than 7.2 µg/L. Since it can be reasonably assumed that there is a practical threshold for the carcinogenicity of formaldehyde in the upper respiratory tract it is therefore concluded, that the proposed AEC provides an acceptable level of protection from these effects.

Based on the reported data suggesting that effects of formaldehyde on internal organs, namely kidneys and testes, are associated with local toxicity, internal effects are unlikely to occur if exposure does not exceed the levels corresponding to the inhalation AEC: The proposed AEC of 0.12 µg/L provides a MoE of 50 to the lowest LOAEC of 6 µg/L for male reproductive effects in rats (no NOAEC est.). The proposed AEC further corresponds to an inhaled dose of approximately 0.01 mg/kg bw/d in working man with 8 h exposure per day, resulting in a MoE of 1500 to the oral NOAEL of 15 mg/kg bw/d for kidney toxicity in rats. Based on the steep dose-response relationship of formaldehyde with an early onset of prominent local effects, these margins are currently considered sufficient to provide adequate protection.

Irritation of the skin and sensitisation were observed following dermal administration of doses considerably lower than the oral NOAEL forming the basis for the Systemic Reference Dose. However, the current methodology is not considered suitable to derive a health-based dermal reference value (AEC dermal). Accordingly, risk assessment for skin irritating and sensitising properties follows the qualitative approach and is based on the respective classification and specific classification limits. As the methodology advances, a quantitative approach to the assessment of risk for local effects of formaldehyde on the skin may become feasible at the product authorisation stage based on the available dose-respone information. For skin irritation, a NOAEC of 0.1 % (w/w) was derived from repeated dermal exposure of mice for 3 and 26 weeks. With regard to allergic reactions of the skin, a NOAEC of 0.005 % is suggested for elicitation in sensitised patients, while EC3 estimates of 0.33-0.96 % (w/w) in different matrices may provide a starting point for assessment of induction.

2.2.1.3. Exposure assessment

Exposure of Professionals

The active substance formaldehyde and the biocidal product (a model formulation with 40% w/w active substance) are produced within the EU. Formaldehyde is applied as aqueous solution for disinfection in private and public health areas.
The following scenarios are covered by the exposure assessment in this report

- wiping and mopping of surfaces (general) in patients' rooms (scenario 1)
- wiping and mopping of surfaces (general) in operating theatres (scenario 2)
- disinfection of surfaces (epidemic) (scenario 3)
- disinfection of rooms by fogging (epidemic) (scenario 4)
- secondary exposure of professionals towards formaldehyde (scenario 5)

Formaldehyde as disinfectant is used routinely for general uses (prophylactic purposes, see scenario 1 and 2) as surface disinfectant and moreover in cases of danger of an epidemic. The professional cleaning staff is trained and has to follow the elaborated instructions in a repetitive scheme.
For general use the disinfectant is applied typically as 0.05 % or ≤ 0.2 % aqueous solutions. In addition, formaldehyde in concentrations of 1.2 % is applied as surface disinfectant in the case of epidemic (scenario 3). Larger surfaces like floors are usually cleaned and disinfected by mopping. Smaller surfaced like tables or boards are wiped with cloths. Mopping is usually performed by using the so-called mop changing technique ("Wechselmoppverfahren").

Wiping and mopping of surfaces (general) in patients' rooms (scenario 1)
The rapporteur based his assessment on the recommendation and field studies of the Institution for Statutory Accident Insurance and Prevention in the Health and Welfare (BGW). It is assumed that one person performs both wiping and mopping in a room. Inhalation exposure is calculated on the basis of task specific parameters using ConsExpo 4.1. The operator is mainly exposed to vapour of formaldehyde during the mixing & loading phase and the application phase (wiping and mopping). The exposure relevant determinants are duration of the task, size of the disinfected area and concentration of formaldehyde solution. The obtained results are valid for workplaces where the operator leaves the room immediately after the disinfection.
Dermal exposure is expected to appear predominantly during the preparation of the disinfectant by dilution due to splashes and while dipping the hand into disinfectant solution during wiping. Post application is assumed during disposal of residues. The mopping is assumed to be performed

by using the so-called mop changing technique ("Wechselmoppverfahren"). Due to this technique a direct contact to the mop or the disinfection solution in the bucket is not expected. However in the case of incidental contact it is expected that the potential dermal exposure will not exceed the level of exposure of the mixing and loading phase. The duration of dermal exposure during mopping and wiping is 330 min per day.

Wiping and mopping of surfaces in operating theatres (scenario 2)
The used models and parameters are the same as in scenario 1 described. The mixing and loading of formaldehyde is considered to be a dilution step from the 40% formaldehyde model product to a 0.2% water based formaldehyde solution. The operator is mainly exposed to vapour of formaldehyde during the mixing & loading phase and the application phase (wiping and mopping). The estimated concentration is obtained for professional use during surface disinfection of 8 times in operating theatres under the assumption that the ventilation rate is 10/h, that surfaces are wiped and mopped for 30 minutes per operating theatre, and that the person leaves immediately the room after disinfection.
Dermal exposure is expected to appear during the preparation of the disinfectant by dilution due to splashes and while dipping the hand into disinfectant solution during wiping. Post-application is assumed during disposal of residues. Due to mop changing technique a direct contact to the mop or the disinfectant solution in the bucket is not expected. However in the case of incidental contact it is expected that the potential dermal exposure will not exceed the level of exposure of the mixing and loading phase. The duration of dermal exposure is in total 240 min. per day.

Disinfection of surfaces (epidemic) (scenario 3)
In epidemic case the number of 10 rooms per day is assessed. The main difference to scenario1 and 2 is the higher concentration of 1.2°% formaldehyde. Application of the diluted solutions takes place via wiping and mopping. Exposure to vapour of 1.2°% formaldehyde is calculated as evaporation from the disinfectant surface in patients' room. A duration of 150 min is taking into account and the assessment is only valid for a professional leaving the room immediately after disinfection.
Dermal exposure is expected to appear predominantly during the preparation of the disinfectant by dilution due to splashes and while dipping the hand into disinfectant solution during wiping. Post application is assumed during disposal of residues.

Disinfection of rooms by fogging (epidemic) (scenario 4)
The following working steps are necessary for fogging with formaldehyde and performed by a disinfector: sealing of the room, dilution of 40 % formaldehyde to a 12 % formaldehyde water based solution and pouring into the fogging device, starting the fogging from outside the room, fogging of formaldehyde solution, starting neutralisation with ammonia solution from outside the room, ventilation of the room, removing equipment and cleaning of the room and the equipment from residues of methenamine (reaction product of formaldehyde and ammonia). For the exposure assessment the exposure to residues the methenamine is not further considered.
Due to self-acting of the fogging (controlled from outside) inhalation exposure to formaldehyde is expected for the mixing, loading. No inhalation exposure is expected for the disinfector during the disinfection phase.
In Germany after 6 hours of fogging ammonia is dispersed immediately for neutralisation for one hour. After neutralisation the disinfector enters the room (with personal protection equipment) to allow the ventilation of the room / opening of windows and then leaves again. Taking into account the neutralisation with ammonia inhalation exposure of the disinfector is not expected assuming a 100% neutralisation of formaldehyde with ammonia.

Dermal exposure is probable during mixing and loading of the fogging equipment. Manual mixing and loading is considered to represent the reasonable worst case. During the application phase the disinfector is not present in the fumigated room. The disinfector enters the room after fogging and neutralisation to open the windows for ventilation purposes. Potential dermal exposure is therefore not expected. A dermal exposure to residues of methenamine may be reasonable but is not assessed here.

Secondary exposure of bystanders towards formaldehyde (scenario 5)

A secondary exposure via inhalation after the regular mopping and wiping process (scenario 1a, 1b, 2) is not expected since a waiting period before re-entry is required. A dermal contact is excluded since surfaces are left to dry after application.

A secondary exposure of professionals during and after mopping and wiping (scenario 3) and fogging in epidemic case (scenario 4) is excluded since the application is restricted to specialised professional users and a waiting period before re-entry is required.

Exposure of Non-Professionals and the General Public

Primary Exposure

Non-professional use of formaldehyde is excluded.

Secondary Exposure

The applicant describes two scenarios, namely fogging and wiping/mopping. In the fogging scenario, the general public is not exposed at all, as fogging is performed by trained professionals only, air concentration is monitored, and the public is only allowed to enter the disinfected rooms when air concentration is below 0.1 mL/m^3. Exposure to the general public may occur (1) by inhalation of formaldehyde evaporating from a wiped or mopped surface and (2) dermally if visitors or patients in hospitals get in contact to surfaces treated with formaldehyde. During application nobody is allowed in the room. Due to the volatile nature of formaldehyde, on dried surfaces no formaldehyde will be left. It is expected that exposure to wet surfaces is a rare, accidental and acute event.

(1) Although during the application time no one has to stay in the room, a potential secondary exposure cannot be excluded. Inhalation exposure might occur but in any case will be lower than the exposure of disinfectors for regular disinfection purposes since surfaces are left to dry after application. In case of epidemic, rooms are closed until the formaldehyde concentration has reached the safe level.

For quantification of formaldehyde concentration in air, the applicant provided measurements showing that after routine room disinfection with 0.05 % solution the formaldehyde concentration did not exceed 0.2 ppm (without ventilation). Wiping and mopping was performed in two model rooms of 7 m^3 (floor: 2.6 m^2) and 76.5 m^3 (floor: 16.2 m^2) with a temperature between 20 and 24°C, humidity between 45 and 60 % and with “no ventilation”. The task duration was 1 to 2 minutes, the amount of used solution was around 10 ml/m^2. Measurements were performed in the middle of the room in about 150 cm height in a time frame of 20 minutes; each single measurement took 30 sec; a continuous measurement was performed for 60 minutes. The following table summarizes the maximum measurement for each of the used solutions (0.05, 0.1, 0.15, and 0.2 %).

Formaldehyde concentration used	Formaldehyde concentration in air [ppm]
0.05 %	0.14
0.10 %	0.19
0.15 %	0.25
0.20 %	0.39

These maximum measurements were achieved between 15 and 45 minutes after application. It can only be speculated to what extent ventilation will affect the air concentration, but it certainly will be lower. It might well be the case that after regular disinfection with 0.05 % formaldehyde solution the air concentration will stay below 0.1 ppm when ventilation is present, but this cannot be deduced from the given information.

(2) For contact to wet surfaces it is assumed that a film of the disinfection solution with a thickness (h) of 0.01 cm covers the whole palm of the hand and completely penetrates the skin (therefore mouthing need not be considered separately). Under these assumptions, systemic dermal exposure for various concentrations is estimated as follows:

Dilution	Systemic exposure (adult) [mg/kg bw]	Systemic exposure (infant) [mg/kg bw]
0.05%	0.036	0.052
0.15%	0.11	0.15
0.2%	0.14	0.20
1.2%	0.86	1.24

Due to neutralisation a deposit of methenamine is present on the surfaces. For the secondary general public exposure assessment the exposure to residues of methenamine is not further considered as it is assumed that the professional user removes residues of methenamine by wet mopping and use of damp cloths.

2.2.1.4. Risk characterisation

Risk Assessment for Professionals

Systemic effects
The risk characterisation for systemic effects of formaldehyde is performed with the AEL approach. In this approach total internal body burden is compared to the $AEL_{long-term}$ of 0.15 mg/kg bw/d. The long-term AEL is taken because repeated exposure at the workplace cannot be excluded for the use of formaldehyde. In the case of formaldehyde the values of acute, medium and long-term AELs are identical, because the frequency of exposure does not significantly influence systemic effects.

The AEL (an internal reference value) is based upon the oral NOAEL of 15 mg/kg bw/day (stomach: hyperkeratosis, ulcerations, atrophy, hyperplasia; renal papillary necrosis) from a 2 year chronic rat-study, and the knowledge of 100 % oral absorption rate. By using a default assessment factor of 100 an $AEL_{long-term}$ of 0.15 mg/kg bw/day is derived for long term exposure towards formaldehyde.

If the total internal body burden is lower than the reference dose, health risks leading to concern are not anticipated.

For scenario 1a (wiping and mopping of surfaces in patients' rooms (0.2 %)), scenario 2 (wiping and mopping of surfaces (general) in operating theatres (0.2 %)) and scenario 3 (disinfection of surfaces (epidemic case) (1.2 %)) actual exposure still exceed the $AEL_{long-term}$. For tier 2 calculation the following risk mitigation measures are taken into account: protective gloves, protective cover all, and mop changing technique for all three scenarios. For scenario 3 RPE is additionally taken into account.
No safe use is identified for these scenarios in the risk characterisation for systemic effects.

Either comparison of potential exposure in scenario 4 (disinfection of rooms by fogging – epidemic case), or comparison of actual exposure in scenario 1b (wiping and mopping of surfaces in patients' rooms (0.05 %)) with the $AEL_{long-term}$ lead to no concern. Therefore a safe use is identified for these scenarios.

Local effects

Inhalation
Due to the high reactivity of formaldehyde, local effects especially after inhalation dominate the toxicity profile of the substance. Thus, in a second approach inhalation exposure as mean event concentrations are compared to the derived AEC in a quantitative risk characterisation for local effects after inhalation.

The AEC (an external reference value) is based upon the NOAEC of 1.2 µg/l for findings of degenerative and pre-neoplastic lesions of nasal mucosa in studies with rats and monkeys. By using an assessment factor of 10, an AEC of 0.12 µg/l (equivalent to 0.1 ppm) is derived for inhalation exposure towards formaldehyde.

If the inhalation exposure as mean event concentration is lower than the external reference dose, health risks leading to concern are not anticipated.

To conclude on the acceptability of the scenarios considered it is essential to know, if the inhalation exposure of the professional user is sequential. In the case of formaldehyde a sequential exposure via inhalation is assumed. Therefore, no safe use is identified for scenario 1a (wiping and mopping of surfaces in patients' rooms (0.2 %)), scenario 1b (wiping and mopping of surfaces in patients' rooms (0.05 %)), scenario 2 (wiping and mopping of surfaces (general) in operating theatres (0.2 %)) and scenario 3 (disinfection of surfaces (epidemic case) (1.2 %)) in the risk characterisation for local effects after inhalation.

For the other professional exposure scenario (scenario 4: disinfection of rooms by fogging (epidemic case)) mean event concentration in the mixing and loading phase is below the AEC and no inhalation exposure is expected in application phase. Thus a safe use is identified for this scenario.

Dermal
Due to the skin sensitizing and skin corrosive properties of formaldehyde, a qualitative risk assessment for local dermal effects as well as semi-quantitative considerations about the sensitizing effects of formaldehyde are necessary. Based on the Guidance for Human Health Risk Assessment, Volume III – Part B, a local dermal risk assessment has been carried out in addition to the quantitative risk characterisations for systemic effects and local effects by inhalation. The local dermal risk assessment takes into account the concentrated biocidal product as well as the different dilutions thereof.

Regarding local dermal effects the active substance formaldehyde is classified as Skin Sens. 1; H317 and Skin Corr. 1B; H314. For classification of the different dilutions of formaldehyde the following specific concentration limits have to be considered:

Skin Corr. 1B, H314: C ≥ 25 %
Skin Sens. 1; H317: C ≥ 0.2 %
Skin Irrit. 2; H315: 5 % ≤C < 25 %
Eye Irrit. 2; H319: 5 % ≤C < 25 %
STOT SE 3; H335: C ≥ 5 %

A dermal NOAEC of 0.005 % for elicitation reactions was derived based on human Patch Test studies. In the study by Flyvhol et al. (1997), twenty formaldehyde-sensitive patients were exposed to concentrations starting from 25 ppm up to 10,000 ppm. At 250 ppm, patient no. 6 (5 %) showed weak reactions and this could be regarded as a LOAEC value. At 50 ppm, an elicitation reaction could not be detected in any of the patients examined (≤ 5 %). Thus, according to this study, 50 ppm could be regarded as a NOAEC value for elicitation.

Concluding qualitatively on the acceptability of risk, the acceptable maximum frequency and duration of potential exposure and potential degree of exposure for the particular hazard category is taken into account (Table 28 from Guidance for Human Health Risk Assessment). For the hazard category "high" the duration of potential dermal exposure should last for few minutes per day or less and a high level of containment, practically no exposure should be achieved.

For scenario 1a (wiping and mopping in patients' rooms (0.2 %)) and scenario 2 (wiping and mopping of surfaces (general) in operating theatres (0.2 %)) the local dermal risk assessment conclude that the scenarios are not acceptable for the following reason. For regular wiping an intensive contact of hands and a long duration of exposure is expected and not acceptable. Thus, the risk of adverse health effects regarding local dermal effects cannot be reduced to an acceptable level. Wiping could be acceptable if it is not performed on a regular basis and is limited to small surfaces (e.g. corners and crevices).
For mopping the mop changing technique prevents the dermal exposure of hands in scenario 1a (wiping and mopping in patients' rooms (0.2 %)) and scenario 2 (wiping and mopping of surfaces (general) in operating theatres (0.2 %)). However, incidental potential body exposure is reasonable. Under the above described prerequisite and that appropriate PPE is worn, the professional user is trained in removing and maintaining the protective clothing/gloves and has a good hygiene practice, the occurrence of exposure during mopping should be considered as acceptable. Assuming this the risk of adverse health effects regarding local dermal effects can be reduced to an acceptable level.
In summary, it is assumed that for scenario 1a (wiping and mopping in patients' rooms (0.2 %)) and scenario 2 (wiping and mopping of surfaces (general) in operating theatres (0.2 %)) dermal exposure could not be reduced as recommended. Thus, the risk of adverse health effects regarding local dermal effects cannot be reduced to an acceptable level.

For scenario 1b (wiping and mopping in patients' rooms (0.05 %)) regular wiping and mopping is acceptable if appropriate PPE is used
Under the described prerequisite and that appropriate PPE is worn, the professional user is trained in removing and maintaining the protective clothing/gloves and has a good hygiene practice, the occurrence of exposure should be considered as acceptable. Assuming this the risk of adverse health effects regarding local dermal effects can be reduced to an acceptable level.

For scenario 3 (disinfection of surfaces (epidemic case) (1.2 %)) it is concluded, that despite of the intensive contact of hands it is assumed that the use of 1.2 % a.s. (hazard category "high") for wiping is acceptable since it is performed only in exceptional cases and not on a regular basis.

Due to the automation of the fogging process the occurrence of dermal exposure is prevented but could occur incidentally in scenario 4 (disinfection of rooms by fogging (epidemic case)). For the mixing and loading and application phase appropriate PPE should be used by the trained professional user. Assuming PPE, good hygiene practice and use of automated fogging system the dermal exposure to formaldehyde can be avoided and the risk of adverse health effects regarding local dermal effects can be reduced to an acceptable level.

Conclusion
The occupational risk assessment for formaldehyde takes into account systemic effects as well as local effects of the active substance. In addition to the systemic risk characterisation which is carried out with the AEL approach a risk characterisation for local effects after inhalation exposure is performed with an AEC as reference value. To assess the local dermal effects of formaldehyde a qualitative risk assessment according to the Guidance for Human Health Risk Assessment, Volume III – Part B is carried out.
In summary, the following table gives an overview of the conclusions of the three different risk characterisations which are carried out for formaldehyde. The acceptability for each scenario in each risk assessment is shown to be able to conclude for the overall assessment of the active substance formaldehyde.

Scenario	Conclusion risk assessment systemic effects	Conclusion risk assessment local effects via inhalation	Conclusion risk assessment local dermal effects	Overall conclusion	Included RMM
1a – wiping and mopping in patients' rooms (0.2 %)	not acceptable	not acceptable	not acceptable	not acceptable	protective gloves, protective

					coverall, mop changing technique, safety goggles
1b – wiping and mopping in patients' rooms (0.05 %)	acceptable	not acceptable	acceptable	not acceptable	same RMM as for 1a
2 – wiping and mopping of surfaces (general in operating theatres (0.2 %)	not acceptable	not acceptable	not acceptable	not acceptable	same RMM as for 1a
3 – disinfection of surfaces (epidemic case) (1.2 %)	not acceptable	not acceptable	acceptable	not acceptable	protective gloves, protective coverall, mop changing technique, safety goggles[1)], RPE
4 – disinfection of rooms by fogging (epidemic case)	acceptable	acceptable	acceptable	acceptable	protective gloves, RPE, safety goggles[1)], automated fogging system

1) In addition safety goggles have to be worn due to local effects if no full face mask as respiratory protective equipment (RPE) is worn. Personal protective equipment (PPE) shall be substituted by engineering, technical and/or administrative equipment according to Dir.98/24/EC and Dir.2004/37/EC if possible.

For the following exposure scenario the risk assessment does not indicate a concern taking into account the above prescribed protection measures: scenario 4: disinfection of rooms by fogging (epidemic case). For detailed description of the required measures please refer to chapter 15.1.2.3. Regarding scenario 4 (disinfection of rooms by fogging (epidemic case), the risk characterisation is considered to be sufficiently comprehensive and reliable. It is essential to indicate, that the conclusion only applies to the active substance in the biocidal product (and not to other ingredients).

For all other scenarios concern is expressed despite the described risk mitigation measures.

Safety Measures for Professionals

For regular disinfection of surfaces in hospitals (scenario 1-2), RPE would be necessary to reduce exposure further. Since gas mask-wearing cleaners would be unacceptable for patients and visitors in hospitals, these scenarios seem unrealistic.

As automated fogging followed by neutralisation with ammonia (scenario 4) is the only scenario without concern, recommendations for personal protective equipment refer to this method if exposure cannot be excluded by other means (e.g. containment):

- Due to local effects, safety goggles, a face shield or a full face mask should be worn during handling of formaldehyde.
- Respiratory protective equipment (RPE) with a protection factor of 20 (full face mask plus gas filter) is necessary and makes up for safety goggles.

- Furthermore, protective gloves are mandatory.

For product authorisation, effective engineering, technical, and/or administrative risk mitigation measures shall be described, e.g.

- Automated mixing and loading (e.g. lost cartridges, dosing pumps etc.), ready-to-use products (instead of concentrates)
- Automated application methods for use of formaldehyde concentration above 0.05%

Risk Assessment for the General Public

The applicant describes two scenarios, namely fogging and wiping/mopping. In the fogging scenario, no health risk for the general public is expected.

In the wiping/mopping scenario patients or the general public may be exposed to formaldehyde evaporating from treated surfaces or by accidental contact to a freshly disinfected surface.

Although during the application time no one must stay in the room, inhalation exposure might occur but in any case will be lower than the exposure of professional disinfectors for regular disinfection purposes since surfaces are left to dry after application. In case of epidemic, rooms are closed until the formaldehyde concentration has reached the safe level.

Measurements provided by the applicant show that the air concentration after regular disinfection with 0.05 % formaldehyde solution will exceed the AEC but not by a great amount. Since the measurements were done without ventilation it might be speculated that the air concentration stays below the AEC when ventilation is present. Information supporting this speculation might be presented when authorising products.

Contact to a surface treated with a 1.2% solution – which is used in case of epidemic only – may poses a health risk for adults. In addition, a health risk for infants touching a surface which is freshly treated with 0.2% solution cannot be ruled out. No health risk is expected when the treatment was performed with a solution of 0.15% or less. This assessment is in line with the classification limit of 0.2 % for sensitisation and the NOAEC of 0.1 % for skin irritation.

Safety Measures for the General Public

As a precautionary measure, after wiping or mopping the general public has to be excluded from treated sites until surfaces are dried to prevent skin contact with freshly treated surfaces. Furthermore, a re-entry waiting time for the general public has to be set and adhered to. The submitted data suggest that a re-entry waiting time of 1 hour is sufficient for well-ventilated rooms. If at product authorisation more details of the measurements are presented it might be possible to reduce this time

2.2.2. Environmental Risk Assessment

The estimation of predicted environmental concentration (PECs) as well as the derivation of predicted non effect concentrations (PNECs) were performed for all relevant environmental compartments according to EU Technical Guidance Document (TGD) on Risk Assessment (2003) and the Emission Scenario Document (ESD) for product-type 2: Disinfectants and algaecides not intended for direct application to humans or animals (RIVM 2001, EC 2011).

2.2.3. Fate and distribution in the environment

Biodegradation

Formaldehyde was shown to be ready biodegradable fulfilling the 10d-window criterion. Nearly the whole dissolved organic carbon (99%) was degraded in a DOC Die-away test (OECD guideline

301A) after 28 days, of which more than 90% DOC have already been degraded on day five. Further supportive information underlines the rapid biodegradation of formaldehyde under different test conditions (OECD 301D, C). In simulation tests of industrial STPs, formaldehyde was eliminated to a high extent under aerobic and anaerobic conditions. Due to the ready biodegradability of formaldehyde, no higher tier degradation studies in water, water/sediment and soil are required.

Abiotic Degradation

Hydrolysis of formaldehyde can be excluded because of the absence of a hydrolysable group in the molecule. At room temperature formaldehyde undergoes complete hydration in water, forming the formaldehyde hydrate methylene glycol. As a hydrate formaldehyde has no chromophore that is capable of absorbing sunlight and thus should not decompose by direct photolysis in water. The UV spectrum of formaldehyde indicates a weak absorption of light at wavelengths between 240 and 360 nm assuming possible direct photolysis of formaldehyde in water and air. However, photolysis in air seems to be of minor importance in comparison to the ready biodegradability of formaldehyde in aqueous medium. In the air compartment, formaldehyde is susceptible to direct photolysis and, in addition, formaldehyde is rapidly degraded via reaction with OH radicals.

Distribution and Mobility

Based on the half-life constants of formaldehyde in air ranging between 0.17 – 1.97 d, accumulation and long range transport in the atmosphere are not expected. The Henry's law constant (0.034 Pa at 25°C) as well as the vapour pressure of formaldehyde in aqueous solutions (187 Pa) is relatively low. Therefore, formaldehyde is not expected to volatilise to air from water surfaces in significant quantities and the amount which reaches the air compartment will be washed out by rain. Unacceptable effects on global warming and stratospheric ozone depletion are not likely. Moreover, formaldehyde is not considered to adsorb onto soil or sediment. The adsorption coefficient (K_{OC}) was estimated to be 15.9 L/kg. Accordingly, only a weak adsorption to sediment or soil and a high mobility in these compartments is assumed

Bioaccumulation

An approximate estimation of the bioconcentration factor in fish and earthworm was performed on basis of log K_{ow} = 0.35 according to the equations given in EU TGD (EC, 2003). Both resulting BCF values were below 1, indicating that formaldehyde has only a low bioaccumulation potential for aquatic and terrestrial organisms. In consequence of the log K_{OW} < 3 and the low estimated BCF values, experimental studies are not required. Moreover, formaldehyde is not surface active or has other properties which point to an intrinsic potential for bioconcentration. With regard to the low estimated BCF values in aquatic and terrestrial indicator species, formaldehyde is not expected to accumulate in the environment.

2.2.4. Effects assessment

Aquatic Compartment

Formaldehyde is toxic to aquatic organisms. The sensitivity of fish, invertebrates and algae, representing the three trophic levels, is nearly identical in short-term tests. The lowest acute LC_{50}/EC_{50} and E_rC_{50} values for these organisms range between 5.7 mg/L for algae and fish and 5.8 mg/L for *Daphnia pulex*. Only one long-term study is available for formaldehyde. In a long-term study on the reproduction of *Daphnia magna* a NOEC of 1.04 mg/L (based on age of first reproduction) was determined. On this basis a $PNEC_{water}$ of 10.4 µg/L was estimated using an assessment factor of 100.

With an EC_{50} value of 20.4 mg/L formaldehyde had a toxic effect on micro-organisms in a sewage treatment plant (STP). The $PNEC_{STP}$ for micro-organisms is 0.2 mg/L.

Sediment

As formaldehyde is not expected to adsorb to sediment (K_{oc} = 15.9/kg), the derivation of a

$PNEC_{sediment}$ is not required.

Terrestrial Compartment

In the absence of valid experimental data with terrestrial organisms, the $PNEC_{soil}$ of 4.16 µg/kg ww was derived from the $PNEC_{water}$ using the equilibrium partitioning method according to the TGD

2.2.5. PBT and POP assessment

Formaldehyde is neither persistent or bioaccumulative nor toxic in terms of the PBT assessment. Formaldehyde is readily biodegradable fulfilling the 10 d-window criterion, the estimated BFC values for aquatic and terrestrial organisms are both less than 1 and the lowest NOEC is 1.04 mg/L. In conclusion, formaldehyde does not fulfil any of the three criteria and is therefore not a PTB substance.

2.2.6. Exposure assessment

For the environmental exposure assessment of the biocidal “dummy” product (b.p.) the following life cycle stages are considered to be relevant:

- production of a.s.,
- application of the b.p. as an aqueous solution for surface disinfection in the medical sector and in industrial areas as well as for room disinfection by fumigation (in hospitals, epidemic).

The representative b.p. is the active substance as manufactured (formaldehyde 40%, cf. Doc III B2) and, therefore, scenario release estimation for the formulation step has been considered unnecessary. The estimations of formaldehyde emissions resulting from its service life as a surface disinfectant are based on the annual formaldehyde tonnage because this approach has been demonstrated to represent the worst-case. For the application of formaldehyde as a surface disinfectant two major environmental exposure pathways have been identified:

- release of waste water containing formaldehyde to the sewer system and subsequently to the STP, surface water, soil and groundwater;
- release of formaldehyde to the atmosphere as a result of volatilization from treated surfaces.

For the application of formaldehyde as a fumigant (epidemic) emissions to the STP and to the surface water have been considered. Even though PEC values have been calculated for the sediment this compartment has been disregarded within the environmental risk characterisation because formaldehyde is not expected to adsorb onto the sediment and the risk characterisation for the sediment compartment is already covered by the risk characterisation of surface water.

Aggregated Exposure Assessment

According to Article 10(1) of the Biocidal Products Directive 98/8/EC substances shall be included in Annex I, IA and IB also taking into account, **where relevant**, cumulative effects from the use of biocidal products containing the same active substance(s). This refers to environmental risk assessment of an active substance contained in different products of the same Product Type (PT) or of different PTs.

Formaldehyde has been originally notified as an active substance for thirteen different biocidal product types (PT 1-6, 9, 11, 12, 13, 20, 22, 23, cf. Regulation (EC) No 1450/2007). However, only six dossiers have been submitted for four different product types, namely, disinfectants in the private area and public health area (PT 2), disinfectants in the area of veterinary hygiene (PT 3), preservatives for food or feedstocks (PT 20) and embalming and taxidermist fluids (PT

22). Two dossiers in product type 20 were dismissed by the EU COM (decision for non-inclusion of formaldehyde in PT 20, CA-Sept12-Doc.4.6).

The need for an aggregated exposure assessment for formaldehyde has been checked applying the "Decision tree on the need for estimation of aggregated exposure" (BIP6.7 Decision Tree Agg Expo). In summary, it has been concluded that no aggregated exposure assessment for formaldehyde has to be performed as the biocidal uses of formaldehyde is less than 10 % of the total tonnage produced. Other uses beyond biocidal uses will mainly contribute to an aggregated exposure of formaldehyde in the environment.

In future, it may become necessary to check the need for aggregated exposure assessment of formaldehyde once again as several formaldehyde releasing reaction products are also notified in the frame of the BPD 98/8/EC.

2.2.7. Risk characterisation

Aquatic Compartment including STP

No unacceptable risks are indicated for surface water and STP when formaldehyde is being used as a surface disinfectant. However, the PEC/PNEC ratio for the exposure scenario "room disinfection" (epidemic) is > 1 for the surface water, indicating that formaldehyde pose an unacceptable risk to aquatic organisms when used as a fumigant (see Doc. II-C, chapter 13).

Terrestrial Compartment including Groundwater

No unacceptable risk is indicated for the soil compartment when formaldehyde is used as a surface disinfection. No emissions to soil occur during room disinfection with formaldehyde and thus no risk characterisation is necessary for this use.

Emissions of formaldehyde to ground water occur via leaching from soil after application of sewage sludge and via atmospheric deposition in the surface disinfection scenario. In a first tier of the ground water assessment it was shown that the legally admissible threshold of 0.1 µg/L as stipulated by Directive 2006/118/EC will be exceeded. Therefore, in a second tier, the ground water assessment was refined by using FOCUS PEARL. The highest derived concentration of formaldehyde in groundwater using FOCUS PEARL was 0.004 µg/L. Hence, a contamination of ground water by formaldehyde in the surface disinfection scenario is not to be expected.

Atmosphere

Emissions to air can occur during the application of formaldehyde for surface disinfection. The estimated $PEC_{local\_air\_ann}$ amounts to 13.27 ng/m^3. However, as no specific effect data is available, no quantitative risk characterisation for the atmosphere was performed. Instead, it was concluded that emissions of formaldehyde to the atmosphere can be neglected due to (i) the low estimated release of the a.s. to air and (ii) the rapid photochemical degradation in air.

Aggregated Risk Assessment

No aggregated risk assessment for formaldehyde in product type 02 has been carried out because the biocidal uses of formaldehyde are less than 10 % of the total tonnage produced (cf. Doc II-B, chapter 8.3.5)

2.2.8. Assessment of endocrine disruptor properties

According to the document "Implementation of scientific criteria to determine the endocrine-disrupting properties of active substances currently under assessment"[2], for reports submitted before 1 September 2013 the provisions of the BPD apply. Furthermore, a maximum approval period of five years is foreseen for substances that fulfil the ED criteria. Since the applicant has no obligation to provide lacking data with respect to the endocrine disruption properties of the active substance, the competent authority has to conclude on the data already provided by the applicant. In case the data is insufficient, the eCA may not be able to draw a comprehensive conclusion on the endocrine disruptor properties of that substance.

Since the evaluation of formaldehyde for PT 2 was submitted before 1 September 2013, requesting additional data would only lead to a delay without being able to finally conclude on the ED properties. Furthermore, formaldehyde already fulfils the exclusion criteria, thus, the regulatory outcome will not change. That means that in line with Article 19(4) of Regulation (EU) No 528/2012, any biocidal products containing formaldehyde will not be authorised for making available on the market for use by the general public. Furthermore, products shall only be authorised for use in Member States where at least one of the conditions set in Article 5(2) of Regulation (EU) No 528/2012 is met. Thus, an assessment of the endocrine disrupting properties according to Regulation (EU) 2017/2100 was not conducted. The endocrine disrupting properties will be assessed in full detail in the scope of the renewal of the approval, where all relevant information can be requested from the applicant.

2.3. Overall conclusions

The outcome of the assessment for formaldehyde in product-type 02 is specified in the BPC opinion following discussions at the 23th and 33th meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA website.

2.4. Requirements for further information related to the reference biocidal product

For the representative biocidal product used as room disinfectant in cases of epidemics an unacceptable risk for the aquatic compartment has been identified. Thus, further tests are required in order to refine the environmental risk assessment for formaldehyde and to demonstrate a safe use:

1. The current effect assessment of formaldehyde is based on three short-term tests (core data set) and one long-term study with invertebrates (cf. Doc II-4). Since a NOEC or EC10 cannot be derived from the submitted algae study, it is advised to conduct a new 72h growth inhibition test with algae with formaldehyde in order to obtain a second long-term effect value (NOEC or EC10) thereby reducing the current assessment factor (AF).

2. A test on the biodegradability of methenamine, which is formed after neutralisation of formaldehyde with ammonia, should be submitted. Proving its ready biodegradability would lead to lower emissions of methenamine to surface water via STP. As a result, the PEC/PNEC ratios of formaldehyde, which is again a hydrolysis product of methenamine in water, would decrease.

3. In order to refine the risk assessment, information on the frequency of epidemics that involve the use of formaldehyde as a fumigant can also be submitted.

[2] See document: Implementation of scientific criteria to determine the endocrine-disrupting properties of active substances currently under assessment (available from https://circabc.europa.eu/ui/group/e947a950-8032-4df9-a3f0-f61eefd3d81b/library/48320db7-fc33-4a91-beec-3d93044190cc/details)

2.5. List of endpoints

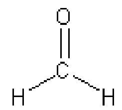
The most important endpoints, as identified during the evaluation process, are listed in Appendix I.

Appendix I: List of endpoints

Chapter 1: Identity, Physical and Chemical Properties, Classification and Labelling

Active substance (ISO Name)	Formaldehyde
Product-type	Bactericide, sporicide, fungicide and virucide

Identity

Chemical name (IUPAC)	Methanal, formaldehyde
Chemical name (CA)	Formaldehyde, methyl aldehyde, formalin, fomol
CAS No	50-00-0
EC No	200-001-8
Other substance No.	156 (CIPAC)
Minimum purity of the active substance as manufactured (g/kg or g/l)	25 – 55.5% in aqueous solution (minimum purity 87.5% with regard to formaldehyde)
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	≤ 7% Methanol
Molecular formula	CH_2O
Molecular mass	30.0258
Structural formula	

Physical and chemical properties

Melting point (state purity)	-118°C to -92°C (formaldehyde gas) -15 °C (formalin (37%))
Boiling point (state purity)	-19.5 °C (1013 hPa) (formaldehyde gas) 96 °C (formalin (37w/w% aqueous solution, containing 10-15% methanol))
Thermal stability / Temperature of decomposition	No decomposition
Appearance (state purity)	colourless gas, pungent suffocating odour (formaldehyde gas) colourless liquid, irritating, pungent odour (formaldehyde solution (30-55% w/w))
Relative density (state purity)	0.815 at - 20°C (formaldehyde gas) 1.1346 g/cm3 at 25°C (aqueous solution: 50% formaldehyde, 7% methanol)
Surface tension (state temperature and concentration of the test solution)	Formaldehyde is not surface active
Vapour pressure (in Pa, state temperature)	5490 hPa, 300 K (formaldehyde gas) 187 Pa, 25°C (formalin (37%))

Henry's law constant (Pa m³ mol -1)	0.034 Pa*m³/mol at 25°C (methanol-free formaldehyde, prepared from 37% formalin)
Solubility in water (g/l or mg/l, state temperature)	pH 5 at ____ ºC: not determined pH 9 at ____ ºC: not determined up to 55% (formaldehyde gas)
Solubility in organic solvents (in g/l or mg/l, state temperature)	
Stability in organic solvents used in biocidal products including relevant breakdown products	
Partition coefficient (log P_{OW}) (state temperature)	0,35 at 25 °C (formaldehyde gas) pH 5 at ____ ºC: pH 9 at ____ ºC: pH *[X]* at ____ ºC:
Dissociation constant	pKa = 13.27 (of hydrate), 25 °C (aqueous solution of formaldehyde; measurement is usually performed with aqueous formaldehyde dilution (for gas or solution))
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	330 (4), 318, (5), 308(5), 298 (4) nm (formaldehyde gas) Lambda maximum (λmax) at 988 nm (aqueous solution: 50% formaldehyde, 7% methanol)
Flammability or flash point	Not flammable
Explosive properties	Not explosive
Oxidising properties	
Auto-ignition or relative self ignition temperature	

Classification and proposed labelling

with regard to toxicological data

Proposed classification of formaldehyde based on Regulation (EC) No 1272/2008

	Classification	Wording
Hazard classes, Hazard categories	Carc. 1B Muta. 2 Acute Tox. 2 Acute Tox. 3 Acute Tox. 4 Skin Corr. 1B Skin Sens. 1A	
Hazard statements	H350i H341 H330	May cause cancer by inhalation Suspected of causing genetic defects Fatal if inhaled

	H311 H302 H314 H317	Toxic in contact with skin Harmful if swallowed Causes severe skin burns and eye damage May cause an allergic skin reaction

Proposed labelling of formaldehyde based on Regulation (EC) No 1272/2008

	Labelling	**Wording**
Pictograms	 GHS05  GHS06  GHS08	
Signal Word	Danger	
Hazard statements	H350 H341 H302 H311 H330 H314 H317	May cause cancer Suspected of causing genetic defects Harmful if swallowed Toxic in contact with skin Fatal if inhaled Causes severe skin burns and eye damage May cause an allergic skin reaction
Suppl. Hazard statements	EUH071	Corrosive to the respiratory tract
Precautionary statements	P201 P202 P272 P281 P301 + P330 + P331 P303 + P361 + P353 P304 + P340 P305 + P351 + P338 P308 + P313 P363 P403 + P233 P405 P501	Obtain special instructions before use Do not handle until all safety precautions have been read and understood Contaminated work clothing should not be allowed out of the workplace Use personal protective equipment as required IF SWALLOWED: rinse mouth. Do NOT induce vomiting IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing IF exposed or concerned: Get medical advice/ attention Wash contaminated clothing before reuse Store in a well-ventilated place. Keep

		container tightly closed Store locked up Dispose of contents/container to …

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	The active substance is determined with the ISO 2227. The principle of the method is reaction of formaldehyde with sodium sulfite, and acidimetric titration of the liberated sodium hydroxide. The second possible method is the DNPH - method. The principle of the method is the derivatisation of formaldehyde with DNPH and the detection with HPLC.
Impurities in technical active substance (principle of method)	The impurity [redacted] is determined with an acid - base titration method. The ASTM Method D 2380-04 is used for the determination of methanol. This method describes the calculation of the methanol content based on the relationship of specific gravity to formaldehyde and methanol content. Additionally the refraction index is measured. Furthermore a GC method used for the determination of methanol is available.

Analytical methods for residues

Soil (principle of method and LOQ)	Not required because of indoor use
Air (principle of method and LOQ)	Residue definition: formaldehyde RP-HPLC-UV; RP18 column LOQ: 0.04 µg/m^3
Water (principle of method and LOQ)	Residue definition: formaldehyde GC-ECD, DB-5 and AT-1701 column, LOQ: 0.08 µg/L (drinking water, US EPA method 556.1); LOQ: 5 µg/L (surface water, US EPA method 556.1)
Body fluids and tissues (principle of method and LOQ)	Monitoring is not meaningful, since formaldehyde is permanently present in humans
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Not required, no relevant residues expected
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Not required, no relevant residues expected

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	100 % uptake, rapid (based on ^{14}C in exhaled air, urine and carcass), systemic bioavailability low (first-pass metabolism)
Rate and extent of dermal absorption*:	100 % uptake (based on ^{14}C in excreta, organs and carcass, and on in vitro data on human skin), systemic bioavailability low (first-pass metabolism)
Distribution:	^{14}C label widely distributed (introduction into C1-pool)
Potential for accumulation:	No evidence for accumulation
Rate and extent of excretion:	Metabolic elimination, high, but variable rate and extent of metabolite excretion (based on 14C) mainly with air and urine (initial plasma t1/2 12 h, terminal t1/2 50 h, 10-40 % 14 C residues after 3-4 d)
Toxicologically significant metabolite(s)	Toxicity of metabolites not assessed separately Urine: formate, hydroxymethylurea

* the dermal absorption value is applicable for the active substance and might not be usable in product authorization

Acute toxicity

Rat LD_{50} oral	640 mg/kg bw	**Acute Tox. 4**
Rat LD_{50} dermal	270 mg/kg bw	**Acute Tox. 3**
Rat LC_{50} inhalation	0.6 mg/L x 4 h	**Acute Tox. 2**

Skin corrosion/irritation	Corrosive	**Skin Corr. 1B**
Eye irritation	Corrosive	**Eye Dam. 1**
Respiratory tract irritation	Yes	
Skin sensitisation (test method used and result)	Sensitising (GPMT, LLNA, human data) EC3 (LLNA):	**Skin Sens. 1A** 0.33-0.96 % (w/w)
Respiratory sensitisation (test method used and result)	no reliable data	

Repeated dose toxicity

Short term

Species / target / critical effect	Rat (oral): Bw ↓; stomach: hyperkeratosis, gastritis; Dog (oral): Bw ↓ Mouse (dermal): Skin: irritation, fissuring, papules Rat (inhalation): Nasal epithelium: degeneration, necrosis, exfoliation, erosion, squamous metaplasia, hyperplasia
Relevant oral NOAEL / LOAEL	28 day, rat: 25 / 125 mg/kg bw/d
Relevant dermal NOAEL / LOAEL	3 wk, mouse: 0.1 / 0.5 % (w/w)
Relevant inhalation NOAEL / LOAEL	21 day, rat: 0.84 / 2.4 µg/L

Subchronic

Species/ target / critical effect	Mouse (dermal): Skin: irritation, fissuring, papules Rat/monkey (inhalation): Nasal epithelium: degeneration, necrosis, exfoliation, erosion, squamous metaplasia, hyperplasia
Relevant oral NOAEL / LOAEL	no reliable data
Relevant dermal NOAEL / LOAEL	26 wk, mouse: 0.1 / 0.5 % (w/w)
Relevant inhalation NOAEL / LOAEL	6-mo, rat / monkey: 1.2 / 3.6 µg/L

Long term

Species/ target / critical effect	Rat (oral): Bw ↓; stomach: hyperkeratosis, ulcerations, atrophy, hyperplasia; kidney: papillary necrosis Rat, mouse (inhalation): Nasal epithelium: rhinitis, dysplasia, squamous metaplasia
Relevant oral NOAEL / LOAEL	2 yr, rat: 15 / 82 mg/kg bw/d
Relevant dermal NOAEL / LOAEL	no data
Relevant inhalation NOAEL / LOAEL	24-mo, rat: <2.4 / 2.4 µg/L
Genotoxicity	Clastogenic locally *in vivo* **Muta. 2**

Carcinogenicity

Species/type of tumour	Rat (inhalation): **Carc. 1B** squamous cell carcinoma of the nasal epithelium
Relevant NOAEL/LOAEL	24 mo, rat: 2.4 / 7.2 µg/L

Reproductive toxicity

Developmental toxicity

Species/ Developmental target / critical effect	Rat, Mouse: Not teratongenic effect
Relevant maternal NOAEL	Rat (inhalation): 24 µg/L x 6 h/d Mouse (oral): 148 mg/kg bw/d
Relevant developmental NOAEL	Rat: NOAEL = 340 mg/kg bw/d (highest dose level tested) Rabbit: NOAEL(embryotoxicity): 300 mg/kg bw/d NOAEL(teratogenicity): 1000 mg/kg bw/d

Fertility

Species/critical effect	Rat: testes atrophy, sperm count and viability ↓, sperm head abnormalities, male fertility ↓, testosterone ↓
Relevant parental NOAEL	no data
Relevant offspring NOAEL	no data
Relevant fertility NOAEL	Rat: < 10 µg/L

Neurotoxicity

Species/ target/critical effect	no data

Developmental Neurotoxicity

Species/ target/critical effect	no data

Immunotoxicity

Species/ target/critical effect	no data

Developmental Immunotoxicity

Species/ target/critical effect	no data

Other toxicological studies

Ocular and respiratory irritation, human:
Eye irritation: ≥ 0.36 µg/L x 4 h with peaks of 0.72 µg/L
Nasal irritation: ≥ 0.6 µg/L x 4 h with peaks of 1.2 µg/L
NOAEC: 0.36 µg/L
population NOAEC: 0.12 µg/L

Medical data

Cohort study: Limited evidence for association of occupational inhalation exposure with increase in SMR for upper respiratory tract cancer (NPC); Increase in RR with peak exposure and average intensity. Patch testing: Incidence of sensitisation ~3 % in dermatitis patients and 1.8 % in workers, NOAEC / LOAEC (elicitation): 0.025 / 0.005 %.

Summary

	Value	Study	Safety factor
$AEL_{long-term}$ $AEL_{medium-term}$ $AEL_{short-term}$	0.15 mg/kg bw/d	Rat, overall (28-d, 90-d, 2-yr)	100
$AEC_{acute, inhalation}$ $AEC_{medium-term, inhalation}$ $AEC_{long-term, inhalation}$	0.12 µg/L	Human, eye irritation (subjective)	3
		Human, overall ocular/respiratory irritation	1[#]
		Rat, Monkey, 6-mo	10[*]
ADI[3]	Not allocated		
ARfD	Not allocated		

MRLs

Relevant commodities	

Reference value for groundwater

According to BPR Annex VI, point 68	

Dermal absorption

Study (*in vitro/vivo*), species tested	*in vivo,* rat and *in vitro,* human
Formulation (formulation type and including concentration(s) tested, vehicle)	aqueous solution (various concentrations and exposure times)
Dermal absorption values used in risk assessment	100 %

[3] If residues in food or feed.

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	Stable, absence of hydrolysable group
pH 5	
pH 9	
Other pH: *[indicate the value]*	
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Stable, absence of chromophore
Readily biodegradable (yes/no)	Yes, fulfilling the 10-d window criterion
Inherent biodegradable (yes/no)	
Biodegradation in freshwater	
Biodegradation in seawater	Not relevant for intended use
Non-extractable residues	Not applicable
Distribution in water / sediment systems (active substance)	Not applicable
Distribution in water / sediment systems (metabolites)	Not applicable

Route and rate of degradation in soil

Mineralization (aerobic)	Not applicable
Laboratory studies (range or median, with number of measurements, with regression coefficient)	Not applicable
DT_{50lab} (20°C, aerobic):	
DT_{90lab} (20°C, aerobic):	
DT_{50lab} (10°C, aerobic):	
DT_{50lab} (20°C, anaerobic):	
degradation in the saturated zone:	
Field studies (state location, range or median with number of measurements)	Not applicable
DT_{50f}:	
DT_{90f}:	
Anaerobic degradation	Not applicable
Soil photolysis	
Non-extractable residues	Not applicable
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	Not applicable

Soil accumulation and plateau concentration	Not applicable

Adsorption / desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	15.9 L/kg (QSAR) [study waiving so far questionable]

Fate and behaviour in air

Direct photolysis in air	Degradation by photolysis is 1.5 times higher than by OH radicals. Worst case assumption: Half time = 1.97 d (see photo-oxidative degradation below)
Quantum yield of direct photolysis	n.a
Photo-oxidative degradation in air	Half life = 1.97 d
Volatilization	n.a

Reference value for groundwater

According to BPR Annex VI, point 68	

Monitoring data, if available

Soil (indicate location and type of study)	Not applicable
Surface water (indicate location and type of study)	Not applicable
Ground water (indicate location and type of study)	Not applicable
Air (indicate location and type of study)	Not applicable

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group)

Species	Time-scale	Endpoint	Toxicity
Fish			
Morone saxatilis	96 h	LC50	5.7 mg/L
Invertebrates			
Daphnia pulex	48 h	EC50	5.8 mg/L

Daphnia magna	21 d	NOEC (age of first reproduction)	1.04 mg/L
Algae			
Desmodesmus subspicatus	72 h	ErC50	5.7 mg/L (geo.mean value from 2 tests)
Microorganisms			
Activated sludge	3 h	EC50	20.4 mg/L

Effects on earthworms or other soil non-target organisms

Acute toxicity to …………………………………..	n.a.
Reproductive toxicity to ………………………..	n.a.

Effects on soil micro-organisms

Nitrogen mineralization	n.a.
Carbon mineralization	n.a.

Effects on terrestrial vertebrates

Acute toxicity to mammals	n.a.
Acute toxicity to birds	n.a.
Dietary toxicity to birds	n.a.
Reproductive toxicity to birds	n.a.

Effects on honeybees

Acute oral toxicity	n.a.
Acute contact toxicity	n.a.

Effects on other beneficial arthropods

Acute oral toxicity	n.a.
Acute contact toxicity	n.a.
Acute toxicity to …………………………………..	n.a.

Bioconcentration

Bioconcentration factor (BCF)	Fish: 0.396 L/kg estimated from log Kow of 0.35 Earthworm: 0.867 L/kg estimated from log

	Kow of 0.35
Depration time (DT_{50})	
Depration time (DT_{90})	
Level of metabolites (%) in organisms accounting for > 10 % of residues	

Chapter 6: Other End Points

Residues in food and feed from intended use of formaldehyde in PT2 biocidal products are not expected. Therefore an additional exposure to humans through diet arising from PT2 use of formaldehyde can be excluded.

Appendix II: List of Intended Uses

Summary of intended uses:

Formaldehyde is a microbiocide which is intended to be used as a disinfectant in industrial, health care and public areas (e.g. hospitals, surgeries, clean room, sanitary facilities, pharmaceutical industries, etc.) in order to circumvent the spread-ing of germs when danger of an infectious disease is given.

Object and/or situation	Member State or Country	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Remarks
				Type	Conc. of as	method kind	number min max	interval between applications (min)	g as/L min max	water L/m² min max	g as/m² min max	
Bactericide, fungicide, virucide	Europe, Germany	n.a. model product	Obligate or facultative pathogenic bacteria, but excluding bacterial spores), fungi and viruses	n.a. model product	a.s. as manufactured (40%)	fumigation	1	1 year (worst-case assumption)	12% ≈ 120 g/L	n.a.	5 g/m³	in cases of epidemic
Bactericide, fungicide, virucide	Europe, Germany					Surface disinfection by mopping	1	1 day	typically: 0.05% ≈ 0.5 g/L some purposes: 0.2% ≈ 2 g/L epidemic 1.2% ≈ 12 g/L	0.01 l/m²	0.0050 - 12g/ m²	

Appendix III: List of studies

Data protection is claimed by the applicant in accordance with Article 60 of Regulation (EU) No 528/2012.

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
	Hose JE, Lightner DV	1980	Absence of formaldehyde residues in penaid shrimp exposed to formalin. Aquaculture 21: 197-201 non GLP, published		
	Kamata, E	1966	Aldehydes in lake and sea waters. Bulletin of the Chemical Society of Japan 39: 1227-1229 *non GLP, published*		
	Murdanoto AP, Sakai Y, Konishi T, Yasuda F, Tani Y, Kato N	1997	Purification and properties of methyl formate synthase, a mitochondrial alcohol dehydrogenase, participating in formaldehyde oxidation in methylotrophic yeasts. Appl. Environ. Microbiol. 63: 1715–1720		
	OECD	2004	Methanol, ICCA documentation on methanol http://cs3-hq.oecd.org/scripts/hpv		
	Offhaus K	1973	Evaluation of waste water purification by analytical procedures (Beurteilung der Abwasserreinigung durch analytische Verfahren). Münchner Beitr. Abwasser-, Fisch.- Flussbiol. 24, 169-196		
	Sills JB, Allen JL	1979	Residues of formaldehyde undetected in fish exposed to formalin. Prog. Fish-Cult. 41: 67-68 non GLP, published		
	Vorholt JA	2002	Cofactor-dependent pathways of formaldehyde oxidation in methylotrophic bacteria. Arch. Microbiol. 178: 239–249 GLP not applicable, published		
IIA 3.1	Benkmann HG, Agarwal DP, Saha N, Goedde HW	1991	Monomorphism of formaldehyde dehydrogenase in different populations. Hum Hered 41(4):276-8, published	No	-
IIA 3.1	Cook RJ, Champion KM, Giometti CS	2001	Methanol toxicity and formate oxidation in NEUT2 mice. Arch Biochem Biophys 393(2):192-8, published	No	-
IIA 3.1	Edman K, Maret W	1990	An MspI RFLP in the human ADH5 gene. Nucleic Acids Res 18(9):2836, published	No	-
IIA 3.1	Edman K, Maret W	1992	Alcohol dehydrogenase genes: restriction fragment length polymorphisms for ADH4 (pi-ADH) and ADH5 (chi-ADH) and construction of haplotypes among different ADH classes. Hum Genet 90(4):395-401, published	No	-
IIA 3.1	Einbrodt HJ, Prajsnar D, Erpenbeck J	1976	Der Formaldehyd- und Ameisensäurespiegel im Blut und Urin beim Menschen nach Formaldehydexposition. Zentralbl Arbeitsmed Arbeitsschutz Prophyl 26(8):154-158, published	No	-

IIA 3.1	Franks SJ	2005	A mathematical model for the absorption and metabolism of formaldehyde vapour by humans. Toxicol Appl Pharmacol 206(3):309-20, published	No	-
IIA 3.1	Heck HD, White EL, Casanova-Schmitz M	1982	Determination of formaldehyde in biological tissues by gas chromatography/mass spectrometry. Biomed Mass Spectrom 9(8):347-53, published	No	-
IIA 3.1	Kimbell JS, Subramaniam RP, Gross EA, Schlosser PM, Morgan KT	2001 a	Dosimetry modeling of inhaled formaldehyde: comparisons of local flux predictions in the rat, monkey, and human nasal passages. Toxicol Sci 64(1):100-10, published	No	-
IIA3.1	Kimbell JS, Overton JH, Subramaniam RP, Schlosser PM, Morgan KT, Conolly RB, Miller FJ	2001 b	Dosimetry modeling of inhaled formaldehyde: binning nasal flux predictions for quantitative risk assessment. Toxicol Sci 64(1):111-21, published	No	-
IIA 3.1	Krupenko SA, Oleinik NV	2002	10-formyltetrahydrofolate dehydrogenase, one of the major folate enzymes, is down-regulated in tumor tissues and possesses suppressor effects on cancer cells. Cell Growth Differ 13(5):227-36, published	No	-
IIA 3.1	Li H, Wang J, König R, Ansari GA, Khan MF	2007	Formaldehyde-protein conjugate-specific antibodies in rats exposed to formaldehyde. J Toxicol Environ Health A 70(13):1071-1075, published	No	-
IIA 3.1	Luo X, Kranzler HR, Zuo L, Wang S, Schork NJ, Gelernter J	2007	Multiple ADH genes modulate risk for drug dependence in both African- and European-Americans. Hum Mol Genet 16(4):380-90, published	No	-
IIA 3.1	Maier KL, Wippermann U, Leuschel L, Josten M, Pflugmacher S, Schröder P, Sandermann H Jr, Takenaka S, Ziesenis A, Heyder J	1999	Xenobiotic-metabolizing enzymes in the canine respiratory tract. Inhal Toxicol 11(1):19-35, published	No	-
IIA 3.1	Mashford PM, Jones AR	1982	Formaldehyde metabolism by the rat: a re-appraisal. Xenobiotica 12(2):119-24, published	No	-
IIA 3.1	Myers JA, Mall J, Doolas A, Jakate SM, Saclarides TJ	1997	Absorption kinetics of rectal formalin instillation. World J Surg 21(8):886-9, published	No	-
IIA 3.1	Neely WB	1964	The metabolic fate of formaldehyde 14-C intraperitoneally administered to the rat. Biochem Pharmacol 13:1137-42, published	No	-
IIA 3.1	The Human Genome Nomenclature Committee	2008	Human Genome Database HGNC ID: 253. http://www.genenames.org/, published	No	-
IIA 3.1	Uotila L	1979	Glutathione thiol esterases of human red blood cells. Fractionation by gel electrophoresis and isoelectric focusing. Biochim Biophys Acta 580(2):277-88, published	No	-
IIA 3.1	Waydhas C, Weigl K, Sies H	1978	The disposition of formaldehyde and formate arising from drug N-demethylations dependent on cytochrome P-450 in hepatocytes and in perfused rat	No	-

			liver. Eur J Biochem 89(1):143-50, published		
IIA 3.2	Bono R, Vincenti M, Schiliro' T, Scursatone E, Pignata C, Gilli G	2006	N-Methylenvaline in a group of subjects occupationally exposed to formaldehyde. Toxicol Lett 161(1):10-17, published	No	-
IIA 3.2	European Chemicals Bureau	2000	IUCLID Dataset, Substance ID: 50-00-0, published	No	-
IIA 3.4	Pesonen M, Jolanki R, Larese Filon F, Wilkinson M, Kręcisz B, Kieć-Świerczyńska M, Bauer A, Mahler V, John SM, Schnuch A, Uter W; ESSCA network	2015	Patch test results of the European baseline series among patients with occupational contact dermatitis across Europe - analyses of the European Surveillance System on Contact Allergy network, 2002-2010. Contact Dermatitis 72:154-163.	No	published
IIA 3.4	De Groot AC, van Joost T, Bos JD, van der Meeren HL, Weyland JW	1988	Patch test reactivity to DMDM hydantoin. Relationship to formaldehyde allergy. Contact Dermatitis 18:197-201.	No	published
IIA 3.4	Flyvholm MA, Hall BM, Agner T, Tiedemann E, Greenhill P, Vanderveken W, Freeberg FE, Menné T	1997	Threshold for occluded formaldehyde patch test in formaldehyde-sensitive patients. Relationship to repeated open application test with a product containing formaldehyde releaser. Contact Dermatitis 36:26-33.	No	published
IIA 3.4	Fischer T, Andersen K, Bengtsson U, Frosch P, Gunnarsson Y, Kreilgård B, Menné T, Shaw S, Svensson L, Wilkinson J	1995	Clinical standardization of the TRUE Test formaldehyde patch. Curr Probl Dermatol. 22:24-30.		published
IIA 3.4	Trattner A, Johansen JD, Menné T	1998	Formaldehyde concentration in diagnostic patch testing: comparison of 1% with 2%. Contact Dermatitis. 38:9-13	No	published
IIA 3.5/ IIA 3.7	McGregor D, Bolt H, Cogliano V, Richter-Reichhelm HB	2006	Formaldehyde and glutaraldehyde and nasal cytotoxicity: case study within the context of the 2006 IPCS Human Framework for the Analysis of a cancer mode of action for humans. Crit Rev Toxicol 36(10): 821-835, published	No	-
IIA 3.6	Speit G, Zeller J, Schmid O, Elhajouji A, Ma-Hock L, Neuss S	2009	Inhalation of formaldehyde does not induce systemic genotoxic effects in rats. Mutat Res. 677(1-2):76-85, published	No	-
IIA 3.8	Li KC, Powell DC, Aulerich RJ, Walker RD, Render JA, Maes RK, Bursian SJ	1999	Effects of formalin on bacterial growth in mink feed, feed consumption and reproductive performance of adult mink, and growth of mink kits. Vet Hum Toxicol 41(4):225-232, published	No	-
IIA 3.8	Odeigah P	1997	Sperm head abnormalities and dominant lethal effects of formaldehyde in albino	No	-

			rats. Mutation Research 389(2-3), 141-148, published		
IIA 3.8	Özen OA, Akpolat N, Songur A, Kus I, Zararsiz I, Ozacmak VH, Sarsilmaz M	2005	Effect of formaldehyde inhalation on Hsp70 in seminiferous tubules of rat testes: an immunohistochemical study. Toxicology and Industrial Health 21(9), 249-254, published	No	-
IIA 3.8	Tang M, Xie Y, Yi Y, Wang W et al.	2003	Effect of formaldehyde on germ cells of male mice. J Hygiene Research 32(6), 544-548, published	No	-
IIA 3.8	Zhou DX, Qiu SD, Zhang J, Tian H, Wang HX	2006	The protective effect of vitamin E against oxidative damage caused by formaldehyde in the testes of adult rats. Asian J Androl 8(5):548-588, published	No	-
IIA 3.8	Zhou DX, Qiu SD, Zhang J, Wang ZY	2006	[Reproductive toxicity of formaldehyde to adult male rats and the functional mechanism concerned]. Sichuan Da Xue Xue Bao Yi Xue Ban 37(4):566-569, published	No	-
IIA 3.9	Lu Z, Li CM, Qiao Y, Yan Y, Yang X	2008	Effect of inhaled formaldehyde on learning and memory of mice. Indoor Air 18(2):77-83, published	No	-
IIA 3.9	Malek FA, Möritz KU, Fanghänel J	2004	Effects of a single inhalation exposure to formaldehyde on the open field behavoir of mice. Int J Hyg Environ Health 207: 151-158, published	No	-
IIA 3.9	Pitten FA, Kramer A, Herrmann K, Bremer J, Koch S	2000	Formaldehyde neurotoxicity in animal experiments. Pathol Res Pract 196(3):193-198, published	No	-
IIA 3.10	Beane Freeman LE, Blair A, Lubin JH, Stewart PA, Hayes RB, Hoover RN, Hauptmann M	2009	Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. J Natl Cancer Inst. 101(10):751-61, published	No	-
IIA 3.10	Commission of the European Communities	2007	COM/07/S5, Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment, FORMALDEHYDE: EVIDENCE FOR SYSTEMIC MUTAGENICITY, published	No	-
IIA 3.11	Bolt HM, Huici-Montagud A	2008	Strategy of the scientific committee on occupational exposure limits (SCOEL) in the derivation of occupational exposure limits for carcinogens and mutagens. Arch Toxicol. 82(1):61-4, published	No	-
IIA 4	EC	2003	Technical Guidance Document (TGD) on Risk Assessment in support of Directive 93/67/EEC on risk assessment for new notified substances, Commission Regulation (EC) No. 1488/94 on risk assessment for existing substances (Parts I, II, III and IV) and Directive 98/8/EC of the European Parliament and the Council concerning the placing of biocidal products on the market. European Commission 2003	No	-
IIB 8	EC	2003	Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Part II; Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. EUR 20418 EN/2	No	published

IIB 8	RIVM	2001	RIVM report 601450008: Supplemment to the methology for risk evaluation of biocides. Emission Scenarios Document for Product Type 2: Private and public health area disinfectants and other biocidal products (sanitary and medical sector)	No	published
IIB 8	EC	2011	JRC Scientific and Technical Reports: Emission Scenarios Document for Product Type 2: Private and public health area disinfectants and other biocidal products	No	published
IIB 8	Bundesgesund heitsamt	1994	Bundesgesundheitsblatt (BGA); 37. Jahrgang, Sonderheft Mai; Carl Heymanns Verlag	No	published
IIB 8	RKI	2007	Liste der vom Robert Koch-Institut (RKI) geprüften und anerkannten Desinfektionsmittel und –verfahren, Stand 31.05.2007; diese Bekanntmachung des RKI wurde auch im Bundesgesundheitsblatt Nr. 10 (Oktober) 2007 veröffentlicht		
IIB 8	EC	2008	European Union Risk Assessment Report Methenamine, CAS No: 100-97-0, http://ecb.jrc.ec.europa.eu/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/methenaminereport065.pdf GLP not applicable, published	No	published
IIB 8	EC	2006	Groundwater Directive (GWD), Council Directive 2006/118/EG on the protection of groundwater against pollution and deterioration	No	published
IIB 8	EC	1998	Drinking Water Directive (DWD), Council Directive 98/83/EC on the quality of water intended for human consumption	No	published
IIB 8	EC	2000	FOCUS groundwater scenarios in the EU review of active substances ". Report of the FOCUS Groundwater Scenarios Workgroup, EC Document Reference SANCO/321/2000 Rev.2	No	published
IIB 8	Klein, M.	2011	Proposals for standard scenarios and parameter setting of the FOCUS groundwater scenarios when used in biocide exposure assessment, FKZ: 360 04 035 Umweltbundesamt Dessau-Roßlau	No	published
IIB 8	EC	1998	Biocidal Product Directive (BPD), Directive 98/8/EC concerning the placing of biocidal products on the market	No	published
IIB 8	ECB	2002	TNsG on Annex I inclusion. Technical Notes for Guidance in Support of Directive 98/8/EC of the European Parliament and the Council Concerning the Placing of Biocidal Products on the Market. Principles and Practical Procedures for the inclusion of active substances in Annexes I, IA and IB, April 2002	No	published
IIB 8	Technical Meeting	2012	BIP6.7 Decision Tree Agg Expo: document: TM III 2012 ENV-item 3f (follow up of TM I 2012 ENV-item 5e); developed in the ongoing UBA project FKZ 3711 63 412 (10/2011 – 04/2014	No	published
IIB 8	EC	2011	JRC Scientific and Technical Reports: Emission Scenarios Document for Product Type 3: Veterinary hygiene biocidal products	No	published

IIB 8	INERIS	2001	Supplemmment to the methodology for risk evaluation of biocides. Emission scenarios document for biocides used in taxidermy and embalming processes (Product type 22)	No	published
IIB 8	CA Meeting	2012	EU COM decision for non-inclusion; document: "CA-Sept12-Doc.4.6	No	published
IIB 8.2.2	BG/BIA		BIA/BG-Empfehlungen zur Überwachung von Arbeitsbereichen [BIA/BG-recommendation for controlling areas of occupation], 2002, BGIA - Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (Institute for Industrial Safety of the German Public Accident Insurances), Flächendesinfekonen in Krankenstationen, 1039	No	published
IIB 8.2.2	BIA	2001	BIA-Report 3/2001, Eickmann, Berechnungsverfahren und Modellbildung in der Arbeitsbereichsanalyse, HVBG, Sankt Augustin, 2001	No	published
IIB 8.2.2	Cherrie, J.W.	1999	The effect of room size and general ventilation on the relationship between near and far-field concentrations, Appl. Occ. And Env. Hyg. Vol. 14(8), 539-546	No	published
IIB 8.2.2	EC	2004	Human Exposure to Biocidal Products (TNsG June 2002), User Guidance Document	No	published
IIB 8.2.2	EC	2002	TNsG Human Exposure Technical Notes for Guidance in Support of Directive 98/8/EC of the European Parliament and the Council Concerning the Placing of Biocidal Products on the Market. Human Exposure to Biocidal Products - Guidance on Exposure Estimation [„Report 2002" http://ecb.jrc.it/biocides**]**	No	published
IIB 8.2.2	Eickmann	2006	Eickmann, Thullner, 2006, Berufliche Expositionen gegenüber Formaldehyde im Gesundheitsdienst [Occupational Exposure to Formaldeyhde in the health service], Umweltmed. Forsch. Prax. 11, no. 6, 363-368	No	published
IIB 8.2.2	Eickmann	2003	Udo Eickmann, 2003, Modellierung der Formaldehydblastung bei Arbeiten im Gesundheitsdienst [Modelling of the formaldehyde exposure when working in the health service], Gefahrstoffe Reinhaltung der Luft, Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege (BGW), Gefahrstoffe Reinhaltung der Luft, 63, no. 7-8, 325-330 (published)	No	published
IIB 8.2.2	HEEG	2008	EC, HEEG opinion on the use of available data and models for the assessment of the exposure of operators during loading of products into vessles or systems in industrial scale – agreed at TM I/08, Ispra – 06.04.2008	No	published
IIB 8.2.2	RIVM	2006	Bremmer et al., RIVM report 320104003/2006: Clenaing Product Fact Sheet – To assess the risks for the consumer	No	published
IIB 8.2.2	RKI	2004	Anforderungen an die Hygiene bei der Reiningung und Desinfektion von Flächen – Empfehlungen, Bundesgesundheitsbl-Gesundheitsforsch-Gesundheitsschutz, 47, 2004	No	published
IIB 8.2.2	RKI	2007	Liste der vom Robert Koch-Institut geprüften und anerkannten	No	published

			Desinfektionsmittel und -verfahren1 Stand vom 15.05.2007 (15. Ausgabe) Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschutz 2007 50:1335-1356		
IIC 12	Api AM, Basketter DA, Cadby PA, Cano MF, Ellis G, Gerberick GF, Griem P, McNamee PM, Ryan CA, Safford R	2008	Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. Regul Toxicol Pharmacol 52:3-23.	No	published
IIC 13	EC	2003	Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Part II; Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. EUR 20418 EN/2	**No**	published
IIC 13	EC	2011	JRC Scientific and Technical Reports: Emission Scenarios Document for Product Type 2: Private and public health area disinfectants and other biocidal products	No	published
IIC 13	EC	2000	IUCLID Dataset, ammonia anhydrous, CAS No. 7664-41-7 based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'.	No	-
IIC 13	EC	2008	Comprehensive Risk Assessment Report for methenamine in the frame of Council Regulation (EEC) No. 793/93, EC 27/05/2008. http://echa.europa.eu/documents/10162/d3cf452f-b948-4d63-a28f-5908ce289ee5	No	-
IIC 13	EC	2006	Groundwater Directive (GWD), Council Directive 2006/118/EG on the protection of groundwater against pollution and deterioration	No	-
IIC 13	EC	2000	FOCUS groundwater scenarios in the EU review of active substances ". Report of the FOCUS Groundwater Scenarios Workgroup, EC Document Reference SANCO/321/2000 Rev.2	No	published
IIC 13	Lyman et al.	1983	Handbook of chemical property estimation methods, McGraw-Hill Inc.; New York	No	published
IIC 13	RIVM	2001	RIVM report 601450008: Supplemment to the methology for risk evaluation of biocides. Emission Scenarios Document for Product Type 2: Private and public health area disinfectants and other biocidal products (sanitary and medical sector)	No	published
IIC 15	German Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BauA)	2008	Research project F 1703, p.56-58 („ProMop"): Arbeitsplatzbelastungen bei der Verwendung von bioziden Produkten: http://www.baua.de/de/Publikationen/Fachbeitraege/F1703.html	No	published
IIC 15	German federal ministry of labour and	2001 (currently	Technical Rules for Hazardous Substances (TRGS) 522 (room disinfection - only in German): http://www.baua.de/nn_16738/de/Theme	No	published

	social affais (BMAS), in particular: Committee for Hazardous Substances (AGS)	upda ted)	n-von-A-Z/Gefahrstoffe/TRGS/pdf/TRGS-522.pdf)		
IIC 15	Human Exposure Expert Group (HEEG	2010	HEEG opinion: Default protection factors for protective clothing and gloves	No	published
IIC 15	Robert-Koch-Institut	2004	Anforderungen an die Hygiene bei der Reiningung und Desinfektion von Flächen – Empfehlungen, Bundesgesundheitsbl-Gesundheitsforsch-Gesundheitsschutz, 47, p.51-61	No	published
IIC 15	UK-Health and Safety Executive (HSE)		Control Guidance G217: http://www.coshh-essentials.org.uk/assets/live/G217.pdf , G312: http://www.coshh-essentials.org.uk/assets/live/G312.pdf	No	published

Section No / Reference No	**Author(s)**	**Year**	**Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published**	**Data Protection Claimed (Yes/No)**	**Owner**
A2.6	Ullmann	2005	Formaldehyde. Authors: Reuss G, Disteldorf W, Gamer AO, Hilt A, in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH Verlag GmbH & Co. KGaA. Online Version. GLP not applicable, published	No	-
A2.10/01	[redacted]	2008	[redacted] unplublished	[redacted]	[redacted]
A2.10/01	Ullmann	2005	"Formaldehyde" in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH Verlag GmbH & Co. KGaA. Online Version GLP not applicable, published	No	-
A2.10/02	[redacted]	2006	[redacted]	[redacted]	[redacted]
A2.10/02	[redacted]	2009	[redacted]	[redacted]	[redacted]
A2.10/02	[redacted]	2008	[redacted] unplublished	[redacted]	[redacted]
A2.10/02	Ullmann	2008	"Formaldehyde" in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH Verlag GmbH & Co. KGaA. Online Version GLP not applicable, published	No	-
A3.1	CRC	2001	CRC Handbook of Chemistry and Physics, Lide DR (Editor), 82[th] edition, CRC Press, Boca Raton, 3-166 GLP not applicable, published	No	-

A3.1	Kirk-Othmer	1994	Kirk-Othmer Encyclopedia of Chemical Technology. 4th edition, Volume 11, John Wiley and Sons, New York, NY, 929-951 GLP not applicable, published	No	-
A3.1	Merck	1996	The Merck Index, Budavari S (Editor), 12th edition, Merck & Co, Inc Whitehouse station, NJ, 717-718 GLP not applicable, published	No	-
A3.1.3	[redacted]	2009	[redacted]	[redacted]	[redacted]
A3.2	Boublik T, Fried V & Hala E	1984	The vapour pressure of pure substances – Selected values of the temperature dependence of the vapour pressures ofsome pure substances in the normal and low pressure region. Physical science data vol. 17. Elsevier, Amsterdam, Netherlands GLP not applicable, published	No	-
A3.2	CRC	2001	CRC Handbook of Chemistry and Physics, Lide DR (Editor), 82th edition, CRC Press, Boca Raton, 3-166 GLP not applicable, published	No	-
A3.2	Yaws CL	1997	Vapor pressure. In: Handbook of chemical compound data for hydrocarbons and organic chemicals, selected data for inorganic chemicals. Gulf Publishing, Houston, Texas, 27-53 GLP not applicable, published	No	-
A3.2.1	Betterton EA & Hoffman MR	1988	Henry´s law constants of some environmentally important aldehydes. Environ. Sci. Technol. 22 (12): 1415 –1418 non GLP, published	No	-
A3.2.1	Staudinger J & Roberts PV	1996	A critical review of Henry´s law constants for environmental applications. Crit. Rev. Environ. Sci. Technol. 26 (3): 205 – 297 GLP not applicable, published	No	-
A3.2.1	Zhou X & Mopper K	1990	Apparent partition coefficients of 15 carbonyl compounds between air and seawater and between air and freshwater; implications for air-sea exchange. Environ. Sci. Technol. 24 (12) : 1864 – 1869 non GLP, published	No	-
A3.3	Merck	1996	The Merck Index, Budavari S (Editor), 12th edition, Merck & Co, Inc Whitehouse station, NJ, 717-718 GLP not applicable, published	No	-
A3.4	Lide DR & Milne GWA	1994	Handbook of data on organic compounds. 3rd edition, CRC Press (vol 1), Boca Raton, 2808-2809 GLP not applicable, published	No	-
A3.4	SDBS	2006	SDBS ^{1}H-NMR No. 9410HPM-02-816 SDBS Web : http://www.aist.go.jp/RIODB/SDBS/ (National Institute of Advanced Industrial Science and Technology) GLP not applicable, published	No	-
A3.4	NIST Spectrometry Data Center	2008 a	Formaldehyde – IR spectrum GLP not applicable, published	No	

A3.4	NIST Spectrometry Data Center	2008 b	Formaldehyde – mass spectrum GLP not applicable, published	No	
A3.4	[redacted]	2009 a	[redacted]	[redacted]	[redacted]”
A3.4	[redacted]	2009 b	[redacted]	[redacted]	[redacted]”
A3.5	Merck	1996	The Merck Index, Budavari S (Editor), 12th edition, Merck & Co, Inc Whitehouse station, NJ, 717-718 GLP not applicable, published	No	-
A3.5	Pickrell JA, Mokler BV, Griffis LC, Hobbs CH & Bathija A	1983	Formaldehyde Release rate coefficients from selected consumer products. Environ. Sci. Technol. 17, 753-757 GLP not applicable, published	No	-
A3.6	Serjeant EP & Dempsey B	1979	Ionisation constants of organic acids in aqueous solution. IUPAC Chemical Data Series No. 23, p. 9 GLP not applicable, published	No	-
A3.7	Merck	1996	The Merck Index, Budavari S (Editor), 12th edition, Merck & Co, Inc Whitehouse station, NJ, 717-718 GLP not applicable, published	No	-
A3.7	Ullmann	2005	Formaldehyde. Authors: Reuss G, Disteldorf W, Gamer AO, Hilt A, in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH Verlag GmbH & Co. KgaA. Online Version. GLP not applicable, published	No	-
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