The World Health Organization (2010) indoor air guideline value on formaldehyde and recent scientific studies

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A short-term (30 min) guideline of 0.1 mg/m$^3$ was recommended for preventing sensory irritation in the general population; it applies to all periods during a day.

Also, the value was considered to prevent cancer.
### Physicochemical properties of FA

<table>
<thead>
<tr>
<th>Properties</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction with</td>
<td>–OH, -NH₂ or = NH, -SH a)</td>
</tr>
<tr>
<td>Melting point</td>
<td>-92°C a,b)</td>
</tr>
<tr>
<td>Boiling point</td>
<td>-19°C a,b)</td>
</tr>
<tr>
<td>Water solubility</td>
<td>400g/L at 20°C a,b)</td>
</tr>
<tr>
<td>Vapour pressure</td>
<td>3886 mmHg at 25°C a,b)</td>
</tr>
</tbody>
</table>

a) WHO 2010  

<table>
<thead>
<tr>
<th>Water solubility</th>
<th>Locations of effects</th>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>eye</td>
<td>NH₃ (ammonia)</td>
</tr>
<tr>
<td></td>
<td>larynx</td>
<td>HCl (hydrogen chloride)</td>
</tr>
<tr>
<td></td>
<td>trachea</td>
<td>CH₂O (formaldehyde)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C₃H₄O (acrolein)</td>
</tr>
<tr>
<td>medium</td>
<td>bronchi</td>
<td>SO₂ (sulfur dioxide)</td>
</tr>
<tr>
<td></td>
<td>bronchioli</td>
<td>Cl₂ (chlorine) Br (bromine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R•CO•Cl (org. acid chlorides)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R•NCO (isocyanates)</td>
</tr>
<tr>
<td>low</td>
<td>bronchioli</td>
<td>O₃ (ozone)</td>
</tr>
<tr>
<td></td>
<td>alveoli</td>
<td>NO₂ (nitrogen dioxide)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>COCl₂ (phosgene)</td>
</tr>
</tbody>
</table>

Shusterman D. Review of the upper airway, including olfaction, as mediator of symptoms. Environ Health Perspect 2002; 110 (suppl.4): 649-653.
Formaldehyde toxicokinetics (WHO 2010)

- Absorbed mainly in the upper airways (>90%)
- Reacts with glutathione (HO-CH₂-SG), proteins, RNA and DNA
- GSH-adduct is oxidized to formate (Km(rats)~ 2.6 ppm)
- Exposure above the Km value, FA increases disproportionate in nasal tissue
- Inhalation causes no increase in blood FA
- T₁/₂~1.5 min in plasma
- Formed endogenously (blood: 2-3 mg FA/L; FA in exhaled air: mean~ 2 ppb and 75th percentile~6 ppb)
New studies on nasal and lung uptake of formaldehyde

At ≥0.1 ppm estimated nasal FA uptake in rats, monkeys and humans is ~99, 87 and 85%, respectively, using anatomically accurate computational fluid dynamics models a)

Toxicodynamic calculations: Bypassing the nose and mouth, FA is mainly deposited in the trachea and no FA reaches the deep lung parts and no FA was predicted to be absorbed into the blood in humans b)


Nasal formaldehyde (FA) metabolism

Inhaled FA (CH$_2$O)

Mucus layer FA (CH$_2$(OH)$_2$) (formaldehyde acetal)

Epithelial cell membrane

CH$_2$(OH)$_2$ → Reacts with DNA and proteins

GSH

HO-CH$_2$-SG

FDH

HCOO$^-$ + GSH

Biomarkers:

• Adducts with mucus layer and cell surface constituents from gene expression$^{1,2}$

• DNA adducts$^3$

• N$^6$-formyllysine$^4$

• Gene expression$^{1,2}$

No adducts outside the nasal cavity from inhalation

New ADME relevant studies since WHO (2010)

1. Rats exposed to 0, 0.7, 2, 6, 10 and 15 ppm 6h/day for 1, 4 or 13 weeks a):

Effects at 0.7 to 2 ppm in nasal epithelial cells:

• CH$_2$(OH)$_2$, DNA-protein cross-links, GSH-FA increased slightly and GSH decreases slightly
• Several ppm FA is required for significant changes
• Genomic changes reflects extracellular changes in CH$_2$(OH)$_2$ and GSH
• FA below 1-2 ppm had no effect on intracellular homeostasis

New ADME relevant studies since WHO (2010)

2. Only exogenous DNA adducts in the nose in rats and monkeys
   Nonlinear DNA adduct formation from exogenous FA b)

3. Only exogenous $N^6$-formyllysine in the nose in rats at $\leq 9$ ppm c)

4. Rats exposed to 10 ppm $^{13}$C-FA for 6 h: No increase in blood $^{13}$C-FA d)

Portal-of-entry effects

I. Sensory irritation of eyes and upper airways

II. Asthma: not supported by the WHO (2010) or recent studies

III. Nasal genotoxicity and cancer
Paustenbach et al. (1997) reviewed all data in animals and humans:

- No eye irritation at 0.5 ppm
- Proposed no irritation at < 0.1 ppm (24 h/day) in the general population.
- No especially sensitive group (including asthmatics) was identified.
- Epidemiological studies: Mixed exposures (less valuable)

Key study by WHO (2010): Lang et al. (2008)\textsuperscript{a}

- Controlled chamber study: 11M and 10 F, age: 18-40 y, exposed for 4 h
- Eye and airway effects: NOAEL 0.5 ppm FA;
- LOAEL 0.5 ppm with peaks at 1 ppm
- AF: 5 and rounding to 0.1 mg/m\textsuperscript{3}. The WHO guideline applies to each 30 min period of the day

\textbf{New chamber study}:

NOAEL 0.7 ppm; LOAEL 0.4 ppm with peaks at 0.8 ppm (hypo- and hypersensitive males) \textsuperscript{b)}

\textsuperscript{b) Mueller JU, Bruckner T, Triebig G. Exposure study to examine chemosensory effects of formaldehyde on hyporsensitive and hypersensitive males. J Arch Occup Environ Health 2013, 86: 107-117.}
Sensory irritation: day after day exposure?

- A 10-day study (1 h/day) in mice with a limonene-ozone mixture b)
- It contained volatile organic compounds and FA a)
- FA accounted for \( \frac{3}{4} \) of the sensory irritation effect a)
- Low to very high sensory irritation effects were studied b)
- No increase in sensory irritation or airflow limitation over repeated exposures and no inflammation was observed b)
- Chamber studies adequately reflect long term effects.

Secondary effects of sensory irritation

Effect of formaldehyde on the respiratory rate in mice

Figure 2  Formaldehyde induced decrease in respiratory rate as per cent decrease from baseline (ΔBPM) in naive BALB/c mice. For all plots, each point represents the mean value of four mice.

Effect of formaldehyde on the expiratory flow rate in mice

Hypoxia

Repetitive obstruction of the upper airways in animals and humans (e.g. obstructive sleep apnoea) causes

Biochemical effects:
1. Activation of NADPH oxidase
2. Xanthine oxidase
3. Mitochondrial chain electron leakage
4. Induction of NO synthase

Pathology:
1. Oxidative stress
2. Inflammation
3. Activation of the sympathetic NS

Clinical effects:
1. Adverse cardiovascular effects
2. CNS impairments
II. Asthma

- FA does not cause asthma in itself a) (except RADS)
- No lung function effects of FA (< 1 mg/m$^3$) in asthmatics and non-asthmatics b)
- Pre-exposure to FA in asthmatics and post exposure to an allergen to which subjects were sensitized showed no consistent increase in allergen sensitivity b)
- No convincing association between FA exposures in homes and schools and asthma in children and adults b,c,d).
- New epidemiological studies:
  - One found a positive association in the group with the lowest (rural) FA exposure (Hulin et al. 2010):
  - Two found no association (Hwang et al. 2011; Kim et al. 2011).
- Meta-analysis (McGwin et al., 2010): Significant association between FA exposure and asthma in children. Most influential studies were the Rumchev et al. (2002) and the Garret et al. (1999) studies.

III. Portal-of-entry genotoxicity and carcinogenicity

Animal studies:
• Nasal genotoxicity is well established non-linear exposure-response relationships)
• Nasal cancer: Key effect in cancer risk assessment by the WHO (2010)

Human studies:
• Portal-of-entry genotoxicity is not that clear
• Nasopharyngeal cancer was mainly based on results from the NCI cohort (Hauptmann et al. 2004).
• New update (Beane Freeman et al. 2013)

Buccal and/or nasal genotoxicity in humans

Increased micronucleus formation (MN):

- **Limited consistency** within and across epidemiological studies a)
- Studies have potential **confounders** a)
- **Controlled exposure** study at 4 h/day for 10 working days at 0.15-0.5 ppm FA with peaks at 0.6 and 1 ppm. Buccal cells: **No significant increase** b) Relevance?
- Where present (WHO, 2010), associated with **high mean and/or high peak exposures** c)

Recent studies:

- **High peak exposures** in recent epidemiological studies d,e)
- **Controlled exposure** study 4h/day for 5 days. FA ≤ 0.7 ppm, peaks up to 0.8 ppm. Nasal epithelial cells: No increase in MN in nasal biopsies: **No remarkable change in gene expression** f)

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Nasal epithelial cell FA-DNA adducts \(^{a)}\) and squamous cell carcinomas (SCCs) in rats exposed 6 h/day, 5 days/week to formaldehyde for \(\geq 2\) years \(^{b)}\)

<table>
<thead>
<tr>
<th>Formaldehyde (ppm)</th>
<th>Exogenous N(^2)-HOC H(_2)-dG/Endogenous N(^2)-HOC H(_2)-dG</th>
<th>Number with SCC/group size (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>0/453 (0)</td>
</tr>
<tr>
<td>0.3</td>
<td>-</td>
<td>0/32 (0)</td>
</tr>
<tr>
<td>0.7</td>
<td>0.011</td>
<td>0/90 (0)</td>
</tr>
<tr>
<td>2</td>
<td>0.033</td>
<td>0/364 (0) Apparent NOAEL</td>
</tr>
<tr>
<td>6</td>
<td>0.19</td>
<td>3/325 (0.9) Apparent LOAEL</td>
</tr>
<tr>
<td>10</td>
<td>0.60</td>
<td>20/90 (22)</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>103/232 (44)</td>
</tr>
<tr>
<td>15</td>
<td>2.79</td>
<td>120/278 (43)</td>
</tr>
</tbody>
</table>

\(^{a)}\) Lu et al. Chem Res Toxicol 2011; 24: 159-161; a single 6 h exposure in rats.

### Nasopharyngeal cancer death in 25,619 workers
Recent update of the US NCI cohort a)

<table>
<thead>
<tr>
<th>Peak exposure level</th>
<th>Average exposure intensity</th>
<th>Cumulative exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppm and P trend</td>
<td>RR (95%CI) and (cases)</td>
<td>ppm</td>
</tr>
<tr>
<td>Non-exposed</td>
<td>4.4 (0.3-54) (2)</td>
<td>“0”</td>
</tr>
<tr>
<td>&gt;0 - &lt; 2.0</td>
<td>RR=1 Reference (1)</td>
<td>0.1 - 0.4</td>
</tr>
<tr>
<td>2.0 - &lt; 4.0</td>
<td>Not applicable (0) Apparent NOAEL</td>
<td>0.5 -0.9</td>
</tr>
<tr>
<td>≥ 4.0</td>
<td>7.7 (0.9-62) (7)</td>
<td>≥ 1.0</td>
</tr>
<tr>
<td>P (0+FA) P (FA)</td>
<td>P=0.10 P&lt;0.005</td>
<td>P=0.16 P=0.09 P=0.07 P=0.06</td>
</tr>
</tbody>
</table>

**Non-linear exposure-response relationships, 5 cancers in one plant**

Based on the Hauptmann et al. (2004) study and now supported by the recent update (Beane Freeman et al. 2013):

No excess NPC at mean concentrations ≤ 1 ppm FA and at peak concentrations below 4 ppm

Effect supported from the rat studies

For the guideline setting, the NOAEL at 1 ppm for histopathological effects in rats was used as point of departure and considered to prevent NPC in humans. Accommodates cell proliferation in rats (LOAEL ~ 2 ppm) and SCC (NOAEL ~2 ppm)
Standardized mortality ratios. The three occupational cohorts used in WHO (2010) have been updated recently

<table>
<thead>
<tr>
<th>Study</th>
<th>NCI cohort (^{a,b}) (N=25,619)</th>
<th>UK cohort (^c) (N=14,014)</th>
<th>US garment workers (^d) (N=11,039)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure (ppm)</td>
<td>Median average intensity: 0.3 and range: 0.01-4.3 15% ≥ 1 ppm 24% had peaks ≥4</td>
<td>Range: 0.1 to &gt;2</td>
<td>Geometric mean: 0.15. GSD: 1.9. Past exposure: Substantial higher</td>
</tr>
<tr>
<td>All cancers</td>
<td>1.08 (RR&lt;1 at top exp)</td>
<td>1.10</td>
<td>0.96</td>
</tr>
<tr>
<td>Nose and sinuses</td>
<td>0.90</td>
<td>0.71</td>
<td>0.00 (O/E: 0/0.95)</td>
</tr>
<tr>
<td>Pharynx</td>
<td>-</td>
<td>1.20</td>
<td>0.88</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>1.84 (95%CI: 0.8-3.5)</td>
<td>0.59 (O/E: 1/1.7)</td>
<td>0.00 (O/E: 0/1.33)</td>
</tr>
<tr>
<td>Larynx</td>
<td>1.23</td>
<td>1.22</td>
<td>0.77</td>
</tr>
<tr>
<td>Lung</td>
<td>1.14(^e)</td>
<td>1.26 (smoking?)</td>
<td>1.04</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>1.42</td>
<td>-</td>
<td>0.95</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>0.85</td>
<td>1.06</td>
<td>1.13</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>0.94</td>
<td>0.99</td>
<td>1.24</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1.02</td>
<td>1.02</td>
<td>1.04</td>
</tr>
<tr>
<td>Lymphatic leukemia</td>
<td>1.15</td>
<td>-</td>
<td>0.71</td>
</tr>
<tr>
<td>Myeloid leukemia</td>
<td>0.90</td>
<td>1.20</td>
<td>1.28 ((\uparrow) 10+ y exp and 20+ y since first exp)</td>
</tr>
</tbody>
</table>

\(^a\) Standardized mortality ratio. Where 95% CI does not include 1, it is indicated by bold and red. \(^b\) NCI updated through 2004 (Beane Freeman et al. 2009; 2013). \(^c\) Coggon et al. (2014). \(^d\) Meyers et al. (2013) \(^e\) RR at highest category: peak (0.77), average intensity (1.0) and cumulative exposure (0.78)
Lymphohematopoietic malignancies

Animal studies:
Not convincing, but if present only ~15 ppm and with a non-linear exposure-response relationship

Human studies:
The WHO (2010) analyzed the studies for:
- Exposure-response relationships?
- If non-linear, apparent NOAEL?
- Establishing levels, which the guideline level has to be below to be contradiction free
### Relative risk (RR) of lymphohematopoietic malignancies in humans \(^a\)

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ppm</td>
<td>Average intensity</td>
<td>ppm</td>
<td>Peak exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.99</td>
<td>1.09</td>
<td>0.53</td>
<td>0.70</td>
<td>2.18*</td>
</tr>
<tr>
<td></td>
<td>0.99</td>
<td>1.09</td>
<td>0.53</td>
<td>0.70</td>
<td>2.18*</td>
</tr>
<tr>
<td>&gt;0-&lt;0.5</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>&gt;0-&lt;2.0 NOEL (?)</td>
</tr>
<tr>
<td>Ref. gr.</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5-&lt;1.0</td>
<td>1.29</td>
<td>1.20</td>
<td>3.62*</td>
<td>1.21</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>1.29</td>
<td>1.20</td>
<td>3.62*</td>
<td>1.21</td>
<td>1.40</td>
</tr>
<tr>
<td>≥ 1.0</td>
<td>1.07</td>
<td>0.71</td>
<td>2.48</td>
<td>1.61</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>1.07</td>
<td>0.71</td>
<td>2.48</td>
<td>1.61</td>
<td>1.49</td>
</tr>
<tr>
<td>P(0+FA)</td>
<td>&gt;0.50</td>
<td>&gt;0.5</td>
<td>0.40</td>
<td>0.40</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>P(FA)</td>
<td>&gt;0.50</td>
<td>&gt;0.5</td>
<td>0.40</td>
<td>0.40</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>P(0+FA)</td>
<td>&gt;0.50</td>
<td>&gt;0.5</td>
<td>0.40</td>
<td>0.40</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td></td>
<td>&gt;0.50</td>
<td>&gt;0.5</td>
<td>0.40</td>
<td>0.40</td>
<td>&gt;0.50</td>
</tr>
</tbody>
</table>

Cumulative exposures (ppm-y) showed no association at all

\(^a\) Sometimes added 95% confidence limits. Figures marked with * and red are significant.

## Occupational related to lymphohematopoietic malignancies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>Benzene, trichloroethylene, agriculture/farmers, abattoir (butcher) workers (viruses?), herbicides and pesticides</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>Agriculture/farmers, abattoir workers (viruses?), EBV</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Benzene (AML&lt;sup&gt;a&lt;/sup&gt;), gasoline (3-5% benzene), ionizing radiation (AML), dioxins (TCDD), butchers (viruses?), agriculture/farmers (CLL), 1,3-butadiene, embalmers and formaldehyde exposed workers, treatment with alkylating agents, rubber industry (CLL, benzene?), arsenic, cigarette smoking (9% of AML?), pesticides</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Engine exhaust, teachers, pesticides,</td>
</tr>
</tbody>
</table>

<sup>a</sup> Acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL).

The WHO (2010) indoor air guideline value

Critical effect: sensory irritation
- NOAEL: 0.5 ppm (now 0.7 ppm), using an AF: 5 and rounding:
- Guideline value: 0.1 mg/m³ (0.08 ppm) (30-min average concentration)

Nasal cancer risk assessment (WHO 2010)
- Point of departure: 1 ppm NOAEL for histopathological effects and nasal cell proliferation in rats; AF: 3 for interspecies variation (local effect) and AF: 2 for variation in the human population: 0.17 ppm (0.2 mg/m³) for prevention of nasal cancer
- Biologically motivated model: 0.25 mg/m³ predicts an additional risk \( \leq 10^{-6} \) for continuous exposure of non-smokers a)

Supporting evaluations of cancer effects
- The 1 ppm point of departure: no interspecies AF (rat is the sensitive species). Being precautionary, AF: 10 for intra human variations, suggesting that 0.1 ppm (0.12 mg/m³) would prevent nasal cancer b)

The guideline accommodates NOAEL for lymphohematopoietic cancers

The guideline has no contradiction with observed results