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

Gunnar Damgård Nielsen PhD, Dr Sc (Pharm)
National Research Centre for the Working Environment, Denmark

Updated: 16.04.2012

- A short-term (30 min) guideline of 0.1 mg/m$^3$ was recommended for preventing sensory irritation in the general population.

- Also, the value was considered to prevent cancer.
Formaldehyde toxicokinetics (WHO 2010)

- absorbed mainly in the upper airways (>90%)
- reacts with glutathione (HO-CH$_2$-SG adduct)
- adduct is oxidized to formate (Km(rats)~ 2.6 ppm))
- at levels above the Km value, levels increase disproportionate in nasal tissue
- inhalation causes no increase in blood FA
- T$_{1/2}$~1.5 min in plasma
- formed endogenously
- blood level is about 2-3 mg/L and FA is found in exhaled air (mean~ 2 ppb; 75th percentile~6 ppb)
- reacts with proteins, RNA and DNA
N. vagus (X)
N. trigeminus (V)
N. Glosso-pharyngeus (IX)

<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.
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
I. Sensory irritation of eyes and upper airways

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)

- 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$^3$. The WHO guideline applies to each 30 min period of the day
- New chamber study: NOAEL 0.7 ppm; LOAEL 0.4 ppm with peaks at 0.8 ppm (hypo- and hypersensitive M)

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 ¾ 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.

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 \(^b\).
- 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 mainly based on the Hauptmann et al. 2004 study

Nasal epithelial squamous cell carcinomas (SCCs) in rats exposed 6 h/day, 5 days/week to formaldehyde for ≥ 2 years \(^{a)}\)

<table>
<thead>
<tr>
<th>Formaldehyde (ppm)</th>
<th>Number with SCC/group size (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/453 (0)</td>
</tr>
<tr>
<td>0.3</td>
<td>0/32 (0)</td>
</tr>
<tr>
<td>0.7</td>
<td>0/90 (0)</td>
</tr>
<tr>
<td>2</td>
<td>0/364 (0) Apparent NOAEL</td>
</tr>
<tr>
<td>6</td>
<td>3/325 (0.9) Apparent LOAEL</td>
</tr>
<tr>
<td>10</td>
<td>20/90 (22)</td>
</tr>
<tr>
<td>14</td>
<td>103/232 (44)</td>
</tr>
<tr>
<td>15</td>
<td>120/278 (43)</td>
</tr>
</tbody>
</table>

New studies on toxicokinetics and gene expression by airborne FA:

- Nasal FA-DNA adduct formation is highly non-linear \(^{a,b,c,d}\)
- Genotoxic and cytotoxic mode of action for nasal cancer \(^{a,b,c,d}\)
- No adduct at distant sites \(^{a,b,c,d}\)
- The toxicokinetic analysis indicated highly non-linear dose-response relationship for increase of exogenous accumulated tissue FA \(^{e}\)
- Decreases nasal glutathione and increases gene expression \(^{e}\)
- Below 1 or 2 ppm FA: No increased risk of nasal cancer or in any other tissue, or effect on FA homeostasis within epithelial cells \(^{e}\)

\(^{a}\) Lu et al. Toxicol Sci 2010, 116, 441-451,
\(^{b}\) Lu et al. Chem Res Toxicol 2011, 24, 159-161,
\(^{c}\) Moeller et al. Chem Res Toxicol 2011, 24, 162-164,
\(^{d}\) Swenberg et al. Toxicol Sci 2011, 120(S1), S130-S145,
\(^{e}\) Andersen et al. Toxicol Sci 2010, 118, 716-731.
### Three largest, recently updated, occupational cohorts, simplified from WHO (2010)

<table>
<thead>
<tr>
<th>Study</th>
<th>NCI cohort (N=25,619)</th>
<th>UK cohort (N=14,014)</th>
<th>US garment workers (N=11,039)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure (ppm)</td>
<td>Average: 0.45, range: 0.01-4.25 23% 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><strong>0.90</strong>&lt;sup&gt;a,b)&lt;/sup&gt;/&lt;strong&gt;1.07&lt;/strong&gt;&lt;sup&gt;c)&lt;/sup&gt;</td>
<td><strong>1.10</strong>&lt;sup&gt;b)&lt;/sup&gt;</td>
<td><strong>0.89</strong>&lt;sup&gt;c)&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nose and sinuses</td>
<td>1.19&lt;sup&gt;b)&lt;/sup&gt;</td>
<td>0.87</td>
<td>0.00 (O/E: 0/0.16)</td>
</tr>
<tr>
<td>Pharynx</td>
<td>-</td>
<td>1.55</td>
<td>0.64</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td><strong>2.10</strong>&lt;sup&gt;b,d)&lt;/sup&gt;</td>
<td>0.50 (O/E: 1/2)</td>
<td>0.00 (O/E: 0/0.96)</td>
</tr>
<tr>
<td>Larynx</td>
<td>0.95&lt;sup&gt;b)&lt;/sup&gt;</td>
<td>1.07</td>
<td>0.88</td>
</tr>
<tr>
<td>Lung</td>
<td>0.97&lt;sup&gt;b)&lt;/sup&gt;</td>
<td><strong>1.22</strong>&lt;sup&gt;c)&lt;/sup&gt;</td>
<td>0.98</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td><strong>1.42</strong>&lt;sup&gt;c)&lt;/sup&gt;</td>
<td>0.70</td>
<td>0.55</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>0.85&lt;sup&gt;c)&lt;/sup&gt;</td>
<td>0.98</td>
<td>0.85</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>0.94&lt;sup&gt;c)&lt;/sup&gt;</td>
<td>0.86</td>
<td>-</td>
</tr>
<tr>
<td>Leukemia</td>
<td><strong>1.02</strong>&lt;sup&gt;c)&lt;/sup&gt;</td>
<td>0.91</td>
<td>1.09</td>
</tr>
<tr>
<td>Lymphatic leukemia</td>
<td><strong>1.15</strong>&lt;sup&gt;c)&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myeloid leukemia</td>
<td>0.90&lt;sup&gt;c)&lt;/sup&gt;</td>
<td>0.89 (exp&gt; 2 ppm)</td>
<td><strong>1.44</strong> († 10 y exp + 20 y since first exp)</td>
</tr>
</tbody>
</table>

---

<sup>a)</sup> Standardized mortality ratio. Where 95% CI does not include 1, it is indicated by bold. <sup>b)</sup> NCI updated to 1994 (Hauptmann et al. 2003); not corrected data. <sup>c)</sup> NCI updated to 2004 (Freeman et al. 2009). <sup>d)</sup> Exact CI: 0.91-4.14.
Nasopharyngeal cancer death in 25,619 workers
The US NCI study a)

<table>
<thead>
<tr>
<th>Peak exposure level</th>
<th>Average exposure intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppm</td>
<td>RR and number of cases/person-y</td>
</tr>
<tr>
<td>Non-exposed</td>
<td>1.00 (Reference) 2/409,074</td>
</tr>
<tr>
<td>&gt;0 - &lt; 2.0</td>
<td>Not obtainable 0/209,815</td>
</tr>
<tr>
<td>2.0 - &lt; 4.0</td>
<td>Not obtainable 0/121,729 NOAEL?</td>
</tr>
<tr>
<td>≥ 4.0</td>
<td>1.83 LOAEL? 7/125,090</td>
</tr>
<tr>
<td>P trend (0+FA conc.)</td>
<td>P=0.04 P&lt;0.001</td>
</tr>
</tbody>
</table>

Non-linear exposure-response relationships
Limitations of the Hauptmann et al. (2004) study

Nasopharyngeal cancer (NPC): Validity?  

- Standardized mortality ratio (SMR): 2.10 (exact 95% CL: 0.91-4.14)
- Six of 10 NPC cases were from one (the Wallingford) of 10 plants.
  - SMR in the Wallingford plant was 10 (4-22) and 0.65 (0.08-2.23) in the combined group of the other nine plants. (NOAEL)
- Many Wallingford cases had a short exposure
- Confounders in the Wallingford plant?
- The study missed 1006 death from the period 1980-94

Consistency with other studies?  

- UK cohort (N=14,014) half of expected NPCs (Coggon et al., 2003)
- The US garment worker cohort (N=11,039) no NPC (Pinkerton et al., 2004)
- US case-control study among embalmers who died from lymphohemato-poietic cancers. Death from NPC OR(95%CL): 0.1 (0.01-1.2) (Hauptmann et al., 2009)

WHO 2010 and nasopharyngeal cancer (NPC)

Based on the Hauptmann et al. (2004) study:

Effect supported from the rat studies

No excess NPC at mean concentrations $\leq 1$ ppm FA and at peak concentrations below 4 ppm

For the guideline setting, the rats NOAEL at 1 ppm for histopathological effects and cell proliferation (below the 2 ppm NOAEL for SCC) was used as point of departure and considered to prevent NPC in humans.
Lymphohematopoietic malignancies

- Animal studies:
  Not convincing, but if present only at 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
Relative risk (RR) of lymphohematopoietic malignancies in humans
average intensity, ppm
(Hauptmann et al. 2003; Freemen et al. 2009) a)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.89 0.99 1.03 1.08 0.33 0.53 1.11-2.6 0.40 0.70 2.04</td>
<td>2.18* 1.01-4.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1-&lt;0.5 Ref. gr.</td>
<td>1.00 1.00 1.00 1.00 1.00 NOAEL 1.00 NOAEL 1.00 1.00 1.00</td>
<td></td>
<td>1.00 NOAEL 1.00 NOAEL 1.00 1.00 1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5-&lt;1.0</td>
<td>1.36 1.29 1.20 1.20 4.59* 1.6-13.2 3.62* 1.4-9.3 1.05 NOAEL 1.21 0.56-2.62 NOAEL</td>
<td>1.37 1.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1.0</td>
<td>1.25 1.07 0.80 0.71 3.06* 0.9-10.4 2.48 0.84-7.3 2.19* 0.9-5.3 1.61 0.76-3.39</td>
<td>1.39 1.49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(0+FA) P(FA)</td>
<td>0.4 &gt;0.50 &gt;0.50 &gt;0.5 0.40 &gt;0.5 0.40 &gt;0.5 0.40 &gt;0.5</td>
<td>0.4 &gt;0.5 0.4 &gt;0.5 0.11 0.43</td>
<td>&gt;0.5 &gt;0.5 &gt;0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) Sometimes added 95% confidence limits. Figures marked with * do not include one.

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(^a)), 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>

\(^a\) Acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL).

The WHO (2010) indoor air guideline value

Sensory irritation is the critical effect, which also prevents cancer
- NOAEL: 0.5 ppm, using an AF: 5 and rounding:
- Guideline value: 0.1 mg/m$^3$ (0.08 ppm) (30-min average concentration)

Prevention of nasal cancer will prevent other types of cancer (WHO 2010)
- Point of departure: the 1 ppm NOAEL for histopathological effects and nasal cell proliferation, using an AF of 3 for interspecies variation (local effect) and an AF of 2 for variation in the human population and thus 0.17 ppm (0.2 mg/m$^3$) would prevent cancer
- Biologically motivated model: 0.25 mg/m$^3$ predicts an additional risk $\leq 10^{-6}$ for continuous exposure of non-smokers a)

Supporting evaluation of cancer effects
- The 1 ppm point of departure was used, but no interspecies AF was used as the rat is the sensitive species. Being precautionary, an AF of 10 was used for intra human variations, suggesting that 0.1 ppm (0.12 mg/m$^3$) would prevent cancer b) and supported by the results from the biologically motivated model a)

Backup slides
## Exposure concentrations in homes and dwellings

<table>
<thead>
<tr>
<th>Area</th>
<th>Type of estimate</th>
<th>Concentration (µg/m³ FA)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU, Canada and USA</td>
<td>Geometric mean, median or average</td>
<td>20-40</td>
<td>(WHO 2010)</td>
</tr>
<tr>
<td></td>
<td>95th percentile</td>
<td>≤ 65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>~170</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>Mean</td>
<td>~30</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>Mean</td>
<td>~240</td>
<td></td>
</tr>
<tr>
<td>EU, Canada and USA</td>
<td>Mean</td>
<td>10-80</td>
<td>Salthammer et al. (2010)</td>
</tr>
<tr>
<td></td>
<td>95th percentile</td>
<td>≤ 100</td>
<td></td>
</tr>
<tr>
<td>EU</td>
<td>Mean</td>
<td>5-50</td>
<td>Sarigiannis et al. (2011)</td>
</tr>
</tbody>
</table>

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>-92⁰C a,b)</td>
</tr>
<tr>
<td>Boiling point</td>
<td>-19⁰C a,b)</td>
</tr>
<tr>
<td>Water solubility</td>
<td>400g/L at 20⁰C a,b)</td>
</tr>
<tr>
<td>Vapour pressure</td>
<td>3886 mmHg at 25⁰C a,b)</td>
</tr>
</tbody>
</table>

a) WHO 2010  
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 
DNA adducts$^{3}$)

HO-CH$_2$-SG 
Gene expression$^{1,2}$)

FDH 

HCOO$^-$ + GSH

Lymphohematopoietic malignancies in animal studies

- **Drinking water studies**\(^{a,b}\): Overall, the drinking water studies showed no increase in lymphohematopoietic malignancies in two well-conducted long-term studies (Til et al. 1989; Tobe et al. 1989). Where significant, the effects were at the high FA levels (Soffritti et al. 2002) and apparently, exposure-response relationships were non-linear. However, these results were from a study with severe limitations (IARC 2006).

- **Inhalation studies**\(^{a,b}\): The occurrence of lymphohematopoietic malignancies in inhalation studies in rats and mice is not convincing (c.f. Kerns et al. 1983; Sellakumar et al. 1985; Kamata et al. 1997). Exposures up to 15 ppm FA.

- **Similar conclusion in a recent review**\(^{c}\)

- **In rats SCC and potentially lymphohematopoietic malignancies**

a) WHO (2010)
b) Nielsen GD, Wolkoff P. Arch Toxicol 2010, 84, 423-446.
Decreased survival may mask development of lymphohematopoietic cancer.

If corrected for survival, only lymphohematopoietic malignancies in the highest exposure group across all inhalation studies in rats and mice, i.e. non-linear exposure-response relationship and NOAEL.

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)
- 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 op to 0.8 ppm. Nasal epithelial cells: No increase in MN
  Nasal biopsies: No remarkable change in gene expression f)

Lymphohematopoietic malignancies in humans?

- Meta-analysis\(^{a)}\) and updated analysis\(^{b)}\) the highest exposure group from each study: Increased RR for leukemia\(^{a,b)}\), especially myeloid leukemia\(^{a,b)}\), and multiple myeloma\(^{a)}\), but not for Hodgkin’s\(^{a)}\), non-Hodkin’s lymphoma\(^{a)}\) and lymphatic leukemia\(^{b)}\).

WHO (2010): If FA driven, a non-linear exposure-response relationship and NOAEL.

- Highly exposed Chinese workers\(^{c)}\) (FA median: 1.3 ppm; 90\(^{th}\) percentile: 2.5 ppm) had decreased lymphocyte, granulocyte, platelet and red blood cell counts. Cultivated blood stem cells had increased monosomy of chromosome 7 and trisomy of chromosome 8 in exposed to a median of 2.1 ppm and a 90\(^{th}\) percentile of 4.1 ppm.

WHO (2010): No exposure-response relationship, high exposures (extreme peaks?), and limited transparency. Later evaluations: Study with severe limitations.\(^{d,e)}\)

- US case-control study in embalmers\(^{k)}\): Among lymphohematopoietic malignancies, myeloid leukemia was associated with embalming. Trend was significant with peak FA exposures (driven by +/- FA).

WHO (2010): Low number of cases in the control groups. No exposure-dependent trend within FA groups. Similar OR in each FA metric group. Limitations in exposure assessment (peaks were estimated). Later publication: additional limitations.\(^{d,j)}\)

Acute leukemia is a bone marrow disease with immature blood cells

Acute myeloid/myelogenous/myeloblastic leukemia (AML) (red, some white cells and platelets)
Acute lymphocytic/lymphatic/lymphoblastic leukemia (ALL) (lymphocytic line)

Genetic damage

- **Chromosomal aberrations** — often translocations, i.e. rearrangement of pieces between two non-homologous chromosomes; AML, e.g. t(8;21), inv(16) and t(15;17), and ALL, e.g. t(9;22), t(12;12), t(1;19), t(17;19) and t(8;14). Normal karyotype in AML (30-50%) and in ALL (20-45%).
- **Gene mutations** — genes controlling crucial signalling pathways and key transcription factors.

Epigenetic changes in transcriptional regulation of tumor suppressor genes and oncogenes

- **DNA methylation** (DNA methyl transferases), e.g. of cytosine to 5-methylcytosine in the CpG (G: guanosine) islands in promoters.
- **Histone modification** — methylation, acetylation/deacetylation, ubiquitylation, phosphorylation, sumoylation and ADP-ribosylation.
- **microRNAs** are regulators, e.g. in cell apoptosis, differentiation and proliferation. They are involved in leukemogenesis and tumour suppression.

Chen J, Odenike O, Rowley JD. Leukaemogenesis: more than mutant genes. Nature Reviews 2010, 10, 23-34
Relative risk (RR) of lymphohematopoietic malignancies in humans peak exposure, ppm
(Hauptmann et al. 2003; Freemen et al. 2009) a)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.99</td>
<td>1.07</td>
<td>1.01</td>
<td>1.06</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>0.04-3.2</td>
<td>0.12-3.6</td>
<td>0.1-3.1</td>
<td>0.1-3.6</td>
<td>0.1-3.1</td>
</tr>
<tr>
<td>0.1-&lt;2.0 Ref. gr.</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00 NOAEL</td>
</tr>
<tr>
<td>2.0-&lt;4.0</td>
<td>1.34 NOAEL</td>
<td>1.17 NOAEL</td>
<td>1.02</td>
<td>1.08</td>
<td>3.28 0.96-11</td>
</tr>
<tr>
<td>≥ 4.0</td>
<td>1.48* 1.04-2.2</td>
<td>1.37* 1.03-1.8</td>
<td>0.95</td>
<td>0.91</td>
<td>3.30 0.98-11</td>
</tr>
<tr>
<td>P(0+FA) P(FA)</td>
<td>0.03* 0.03*</td>
<td>0.04* 0.02*</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>0.009* 0.04*</td>
</tr>
</tbody>
</table>

a) Sometimes added 95% confidence limits. Figures in red and marked with * do not include one.

Other risk assessment approaches

- Index report
- France
- US EPA