Systemische toxiciteit van formaldehyde

het belang van endogene vorming en van exogene piekblootstelling

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CGC/NVT, 18 maart 2021

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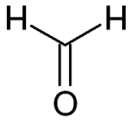
Toxicity profile of formaldehyde

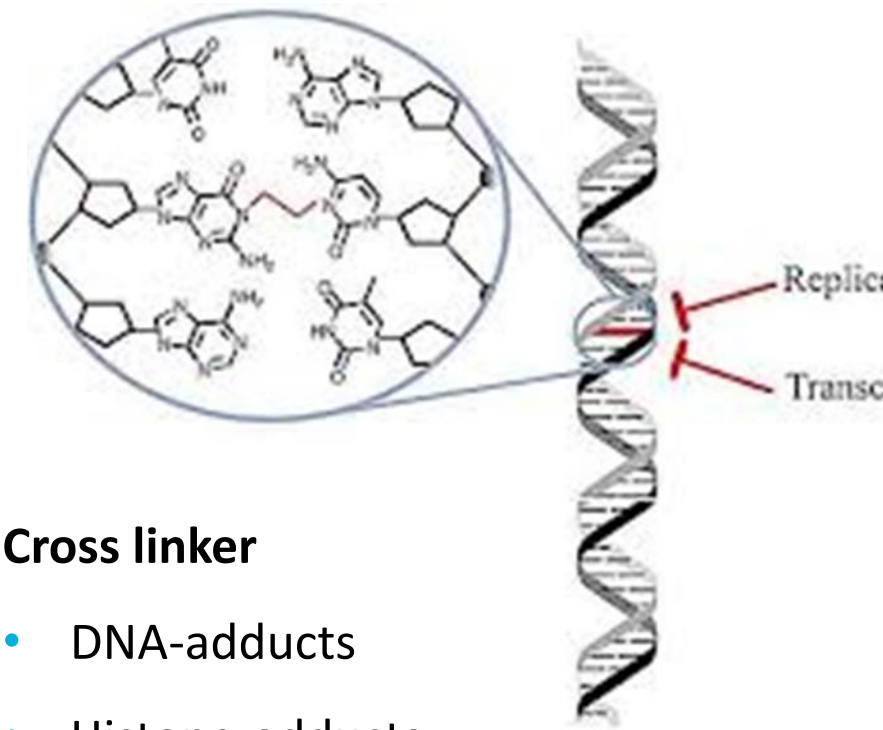
Local

- Sensory irritation of airways
- Irritative and allergic dermatitis
- Tumors of the nose and nose sinuses



Systemic

- Lympho-haemopoietic Cancer (LHC)
- Reproductive toxicity



Cross linker

- DNA-adducts
- Histone-adducts
- DNA-protein cross links (DPC)

Formaldehyde; Health-based recommended occupational exposure limit (HBR-OEL)

- "… This implies that the DECOS considers a health based occupational exposure level (HBR-OEL) of 0.15 mg/m^3 (0.12 ppm) (see page 69) formaldehyde low enough to protect workers against nasal tissue damage, **and as a consequence, also against the potential risk of nasal cancer**.'

- "... To **avoid peak exposures** possibly entailing cytotoxicity-induced hyperproliferation and metaplasia of the nasal respiratory epithelium, DECOS recommends for formaldehyde a short-term exposure limit (STEL)"

- "The committee concluded that the total body of evidence indicates that 0.5 mg/m^3 is an exposure level which is **low enough to avoid significant sensory irritation from short term exposures** and thus, more importantly, **also will be low enough to avoid nasal cytotoxicity from such short exposures.**"

No. 2003/02OSH, The Hague, 27 January 2003.
https://www.gezondheidsraad.nl/documenten/adviezen/2003/01/27/formaldehyde

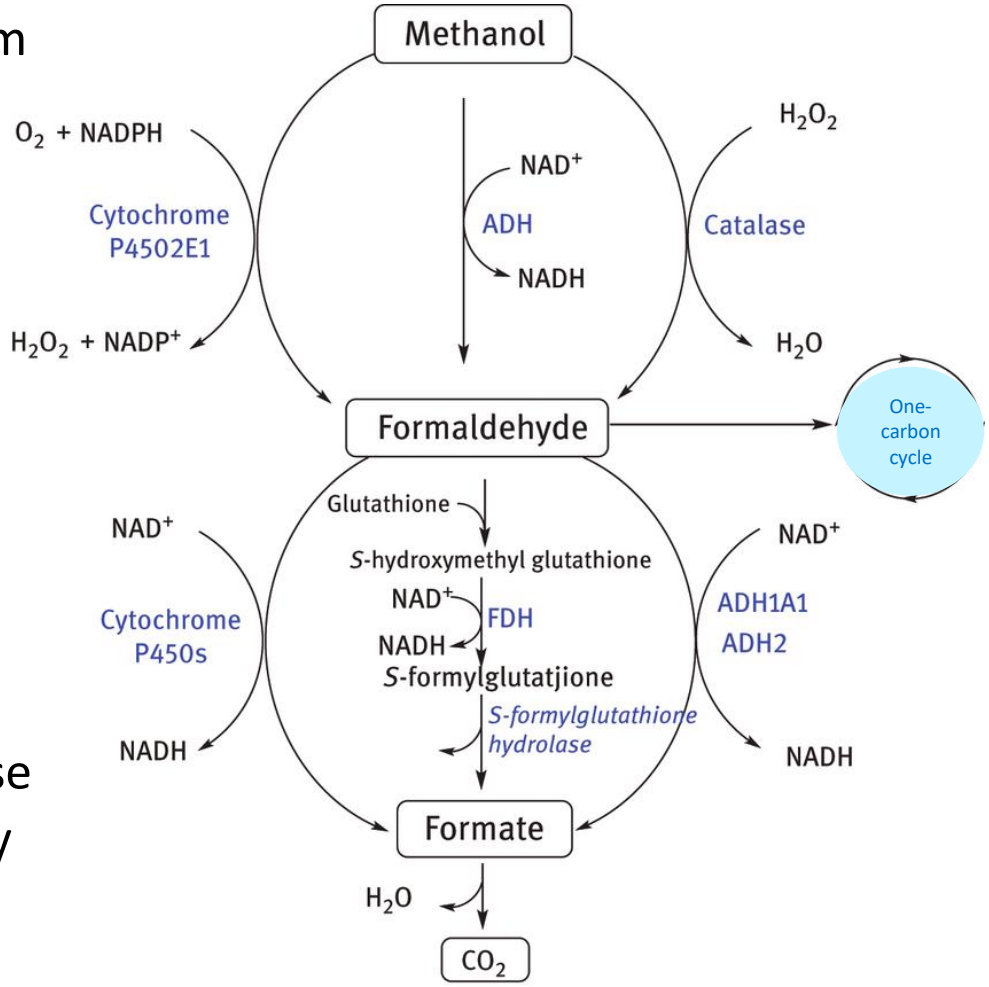
Exogenous Formaldehyde

Exogenous exposure may arise from exposure in the general environment:

- Outdoor air
- Indoor air
- Consumer products
- Open fire
- Road vehicle exhaust

Sources of occupational exposures are:

- Industrial manufacturing and use
- Professional use e.g. in anatomy and pathology laboratories



Modified from J.R. Kuykendall (2010) Comprehensive Toxicology

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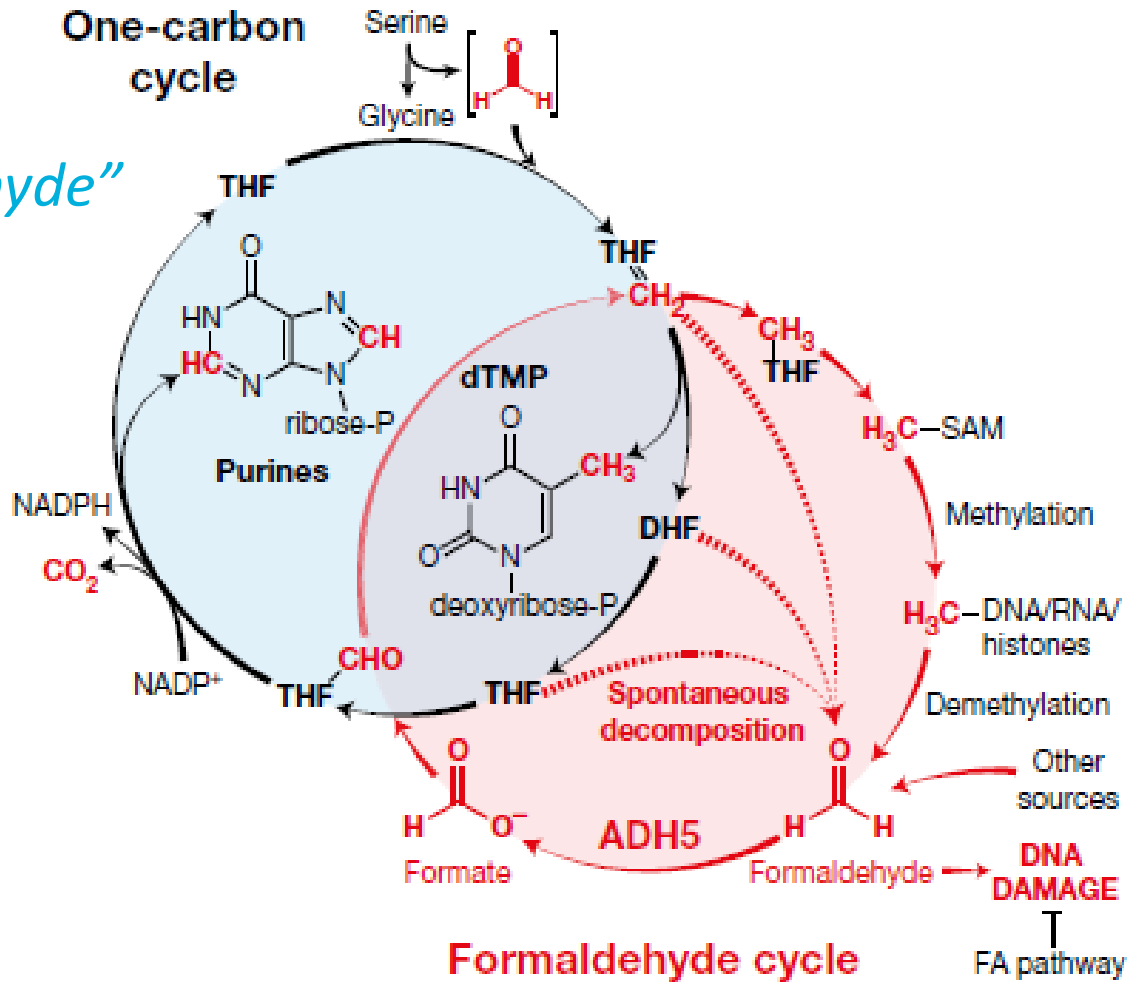
Endogenous formaldehyde cycle

"We live with formaldehyde"



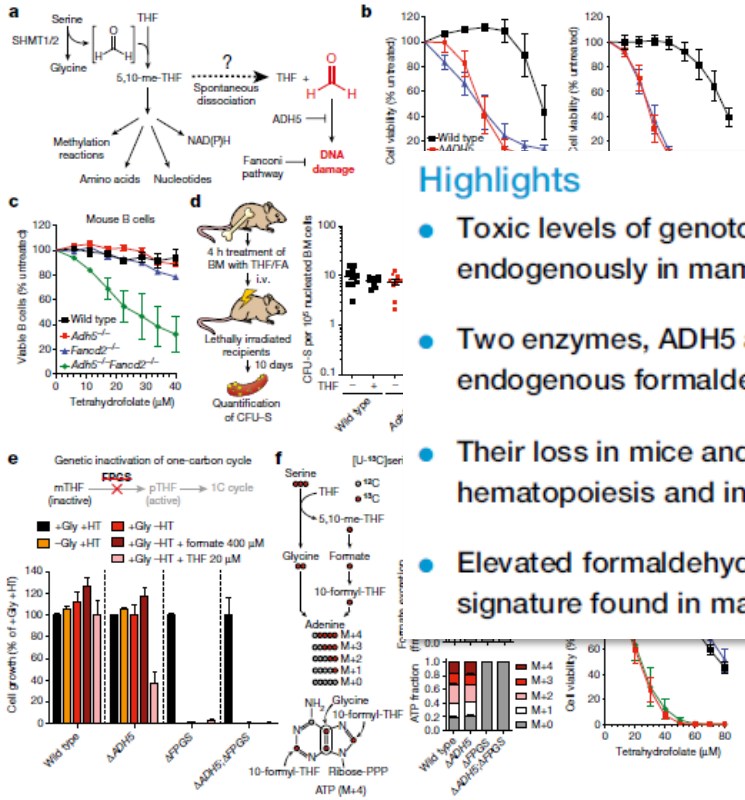
Legend

DHF	= dihydrofolaat
dTMP	= thymidylate
THF	= tetrahydrofolate
THF–CHO	= 10-formyl-THF
THF–CH_3	= 5-methyl-THF
SAM	= S-adenosylmethionine
FA	= Fanconi anaemia

Burgos-Barragan et al. Nature. 2017 Aug 31;548(7669):612. https://doi:10.1038/nature23481

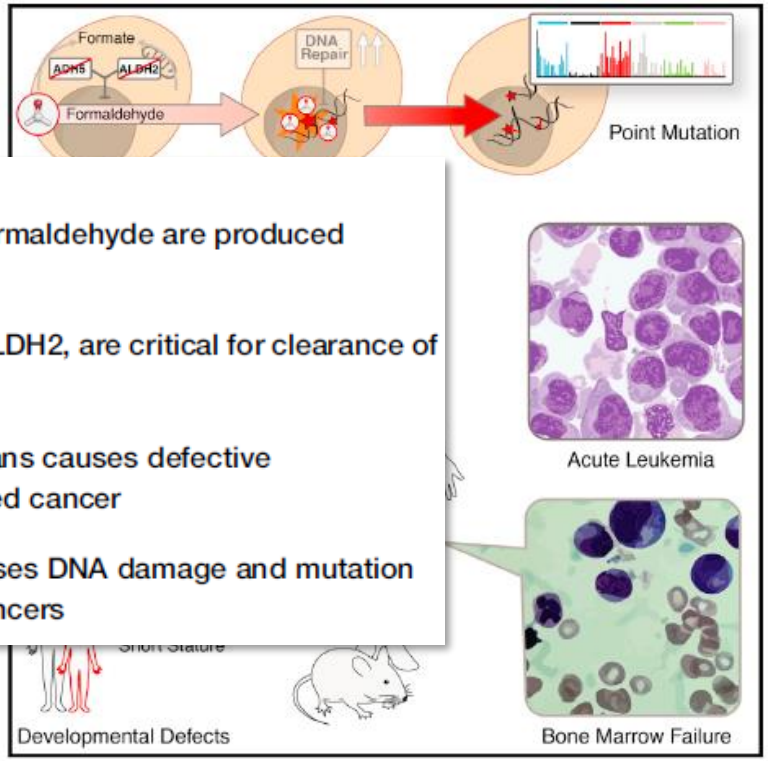
Endogenous* formaldehyde toxicity

Mammals divert endogenous genotoxic formaldehyde into one-carbon metabolism



Burgos-Barragan et al. Nature. 2017 Aug 31;548(7669):612. https://doi:10.1038/nature23481

Two Aldehyde Clearance Systems Are Essential to Prevent Lethal Formaldehyde Accumulation in Mice and Humans



Dingler et al., 2020, Molecular Cell *80*, 996–1012
December 17, 2020 © 2020 MRC Laboratory of Molecular Biology. Published by Elsevier Inc.
https://doi.org/10.1016/j.molcel.2020.10.012

Highlights

- Toxic levels of genotoxic formaldehyde are produced endogenously in mammals
- Two enzymes, ADH5 and ALDH2, are critical for clearance of endogenous formaldehyde
- Their loss in mice and humans causes defective hematopoiesis and increased cancer
- Elevated formaldehyde causes DNA damage and mutation signature found in many cancers

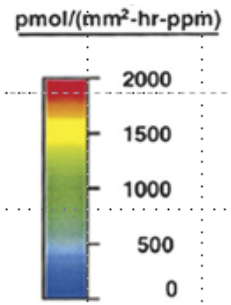
*originating e.g. from histone demethylation and folic acid decomposition

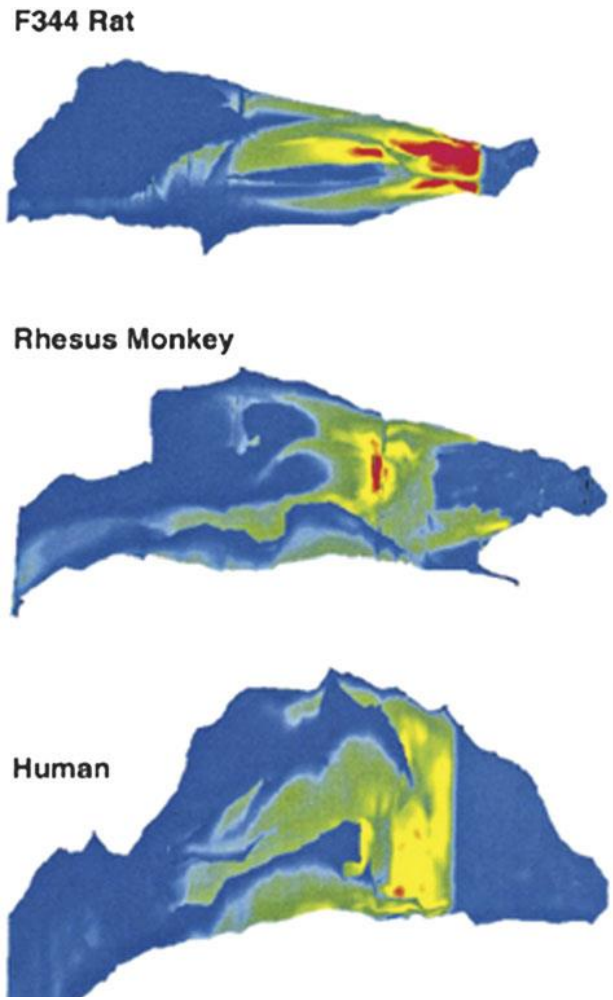
Local effect of inhaled formaldehyde

Nasal wall flux spectra of inhaled formaldehyde simulated in rats, monkeys and humans at normal inspiratory flow rates.

The deposition pattern corresponds to tumor locations

Nose tumors are more frequently observed than tumors of the nose sinuses

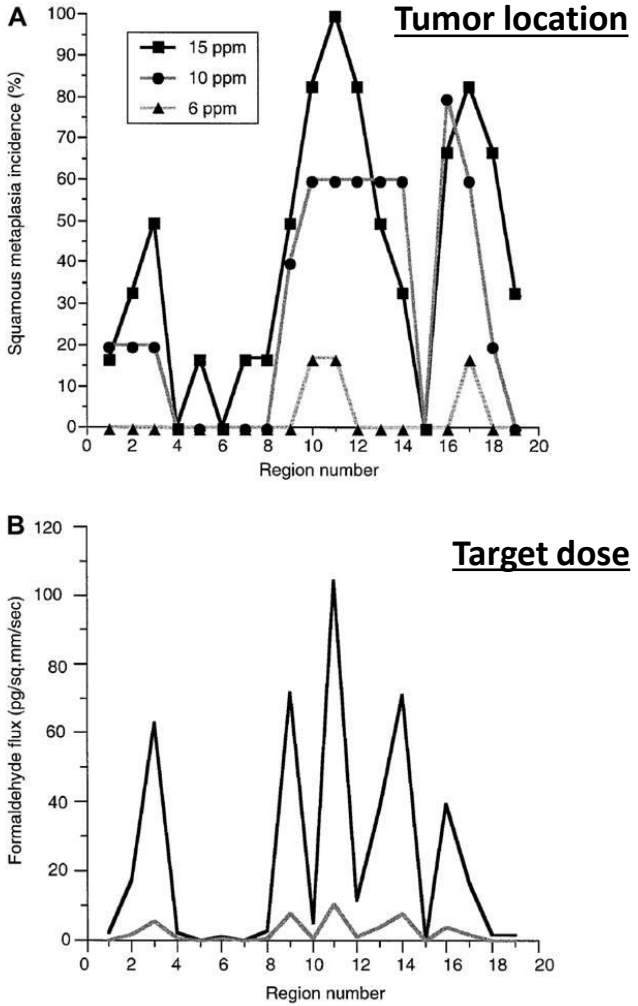




Source: Kimbell et al. (2001) Toxicol Sci 64:100-110.

Nose-only exposure of rats

Observed deposition pattern corresponds to nose tumor locations



Evaluaties neus- en neusbijholtekanker

Expert groep	Classificatie	Doelorgaan	Causaliteit	Veilige grens
Gezondheids-raad, 2003	Geen uitspraak	Neuskeelholte en de neusbijholte	Beperkt bewijs	Onder 0,150 mg/m^3 zijn werknemers voldoende beschermd tegen kanker
IARC, 2012	Groep 1 -Formaldehyde is kankerverwekkend voor de mens	Neus-keelholte	Voldoende bewijs voor oorzakelijk verband	Geen uitspraak
		Neusbijholte	Positieve associatie (maar geen causaliteit)	Geen uitspraak
US-EPA 2010 (openbaar concept)	Groep B1 - Waarschijnlijk kankerverwekkend op basis van beperkt bewijs in de mens	Tumoren van de neus- en keelholte	Beperkt bewijs voor een associatief verband in humane studies en voldoende bewijs in dierstudies	Geen uitspraak
NRC, 2014	Bevestigd als oorzaak van kanker	Neus-keelholte	Causaliteit is bevestigd	Geen uitspraak
		Adenocarcinoma en plaveiselcel- carcinoma in de neusholte en neusbijholte	Bewijs voor een causaal verband op basis van humane studies is consistent	Geen uitspraak
SCOEL 2016	Genotoxisch maar met een drempel-waarde (Groep C)	Neuskeelholte	Sterk bewijs voor mutageniteit en een oorzakelijk verband in dierstudies	Alleen boven 0,369 mg/m^3 mogelijk verhoogd risico

Classification for cancer (IARC 2015)

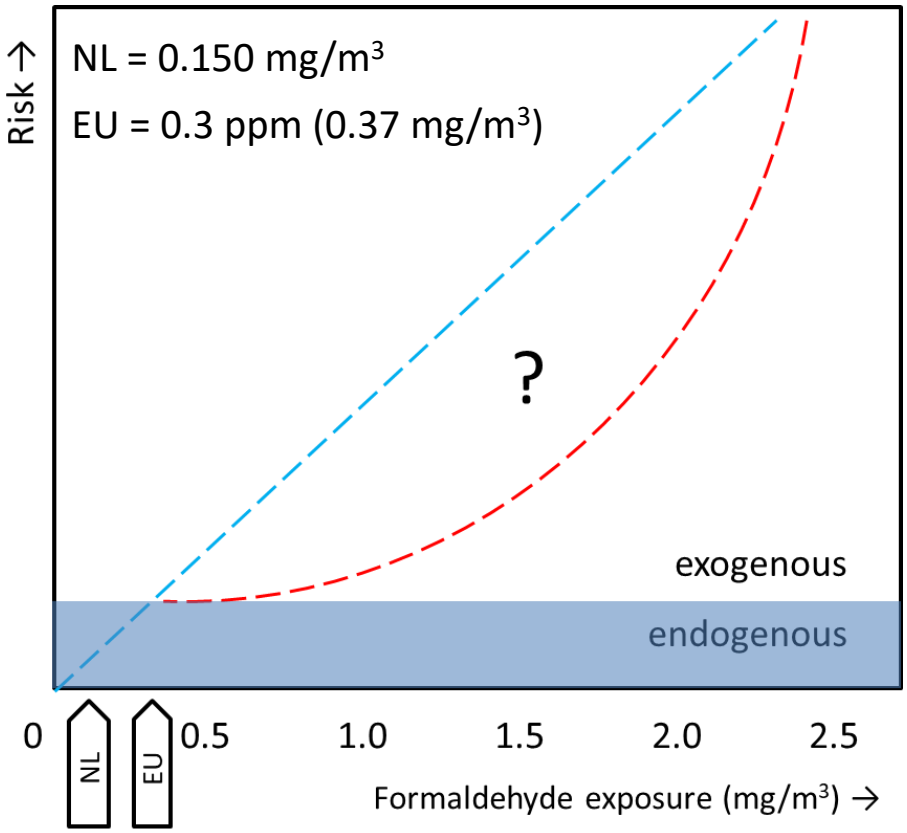
- The current data strongly indicate that **genotoxicity** plays an important role in the carcinogenicity of formaldehyde in **nasal tissues** in humans, and that cellular replication in response to formaldehyde-induced **cytotoxicity** promotes the carcinogenic response.

- **Three possible mechanisms, all focused around genotoxicity**, are moderately supported as the underlying mechanism for induction of **haematological malignancies** in humans. Further research is needed to decide which of the mechanisms is the most important.

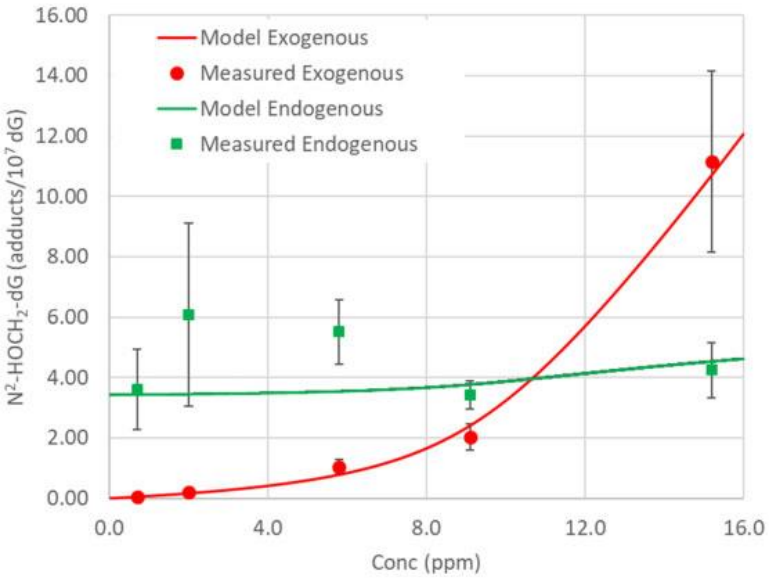
- The Working Group was **not in full agreement** on the evaluation of **formaldehyde causing leukaemias** in humans, with a small majority viewing the evidence as sufficient of carcinogenicity and the minority viewing the evidence as limited.

IARC Monograph 100F (2015) WHO, Lyon, France
https://belglas.files.wordpress.com/2016/01/mono100f-29.pdf

Should formaldehyde be treated as threshold or non-threshold risk?



DNA-adducts in rat nasal tissue



Predictions of the formaldehyde pharmacokinetic model for endogenous (square) and exogenous (circle) formaldehyde DNA-adducts in rat nasal tissue after a single 6-hour exposure to labeled formaldehyde concentrations of 0.7, 2, 6, 9, and 15ppm (data from Lu et al., 2011).

Lu et al (2011) Chem Res Toxicol 24, 159–161
Campbell et al (2020) Tox. Sci. 177(2), 325–333

Endogenous versus exogenous formaldehyde–induced DPC

Rats inhaled clean air during 4d (control) or 15 ppm of [$^{13}CD_2$]-formaldehyde during 1d, 2d or 4d; Outcome: single amino acid–nucleoside crosslinks (dG-Me-Cys);

Tissue	Exposure period (days)	dG-Me-Cys (crosslink/10^8 dG)	
		Endogenous	Exogenous
Nasal	4	6.50 ± 0.30 ($n = 5$)	ND
	1	4.42 ± 1.10 ($n = 6$)	5.52 ± 0.80
	2	4.28 ± 2.34 ($n = 6$)	4.69 ± 1.76
	4	3.67 ± 0.80 ($n = 6$)	18.18 ± 7.23
PBMC	4	4.98 ± 0.61 ($n = 5$)	ND
	1	3.26 ± 0.73 ($n = 4$)	ND
	2	3.00 ± 0.98 ($n = 5$)	ND
	4	7.19 ± 1.73 ($n = 5$)	ND
Bone marrow	4	1.64 ± 0.49 ($n = 4$)	ND
	1	1.80 ± 0.47 ($n = 4$)	ND
	2	1.84 ± 0.61 ($n = 4$)	ND
	4	1.58 ± 0.38 ($n = 4$)	ND

ND = Not detected; PBMC = peripheral blood mononuclear cells

Lai et al. (2016) Cancer Res. 2016 May 1;76(9):2652-61

Endogenous and exogenous formaldehyde–induced DNA adducts

Levels of endogenous and exogenous N^2-HOMe-dG (adducts/10^7 dG) in rat tissues exposed to [$^{13}CD_2$]-formaldehyde (1 and 30 ppb) for 28 day.

nd = not detected

Note: 300 ppb was also tested but results are not shown here

Tissues	Air control		1 ppb		30 ppb	
	Endogenous	Exogenous	Endogenous	Exogenous	Endogenous	Exogenous
Nasal Mucosa	3.23±0.85	nd[b]	3.59±0.90	nd	3.27±0.76	nd
Bone Marrow	4.83±1.54	nd	4.32±1.21	nd	5.03±1.71	nd
PBMC	2.64±1.03	nd	2.72±0.73	nd	2.80±1.11	nd
Trachea	3.14±0.61	nd	3.23±1.02	nd	3.34±0.75	nd
Liver	2.48±0.21	nd	2.57±0.31	nd	2.44±0.34	nd
Hippo campus	2.35±0.56	nd	2.62±0.74	nd	2.52±0.82	nd
Olfactory Bulbs	2.51±0.62	nd	2.74±1.05	nd	2.84±0.45	nd
Cerebellum	2.45±0.76	nd	2.62±0.67	nd	2.46±0.43	nd
Lung	5.25±3.23	nd	3.72±2.20	nd	4.79±3.22	nd

Leng et al. (2019) Arch Toxicol. 93(3):763-773..

Meta analyses of all blood cancers

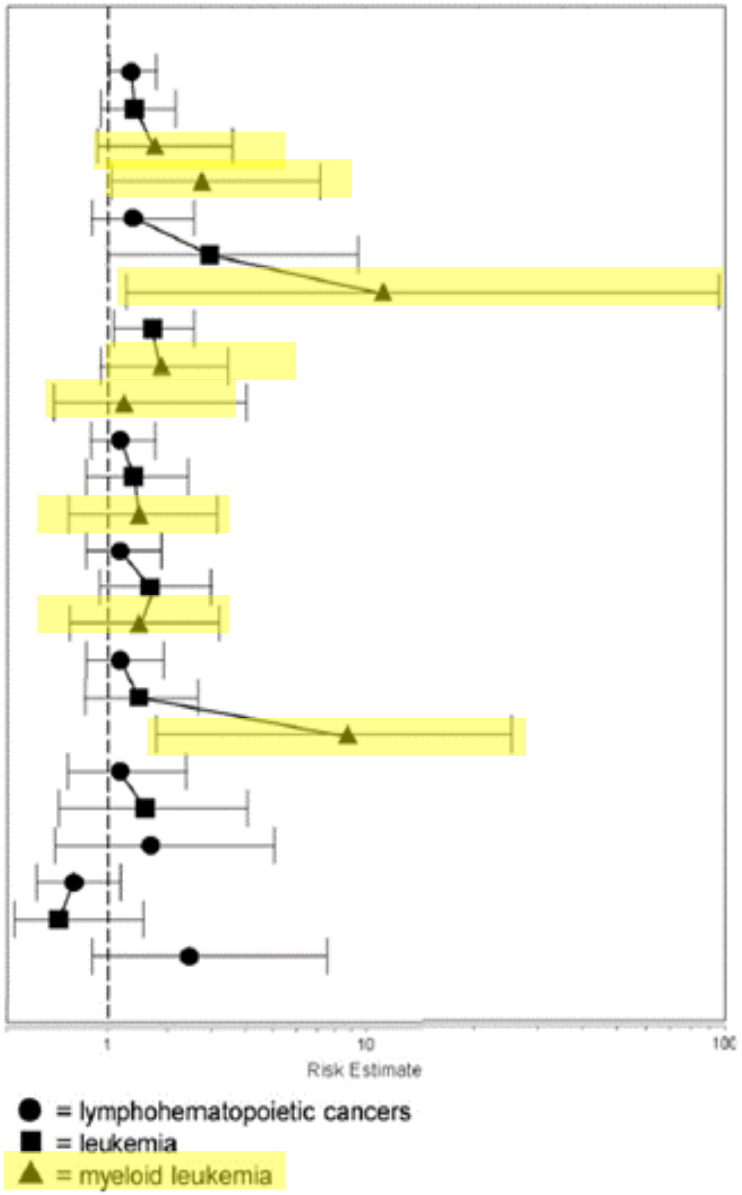
Meta-analyses of all blood cancers and leukemia associated with formaldehyde. Industry and use by anatomists, pathologists and embalmers (professionals)

	Zhang et al., 2009				Bosetti et al., 2008			
Blood cancer type	*N*	*n*	RR	95% CI[a]	*N*	*n*	RR	95% CI
All types	19	392	1.25	1.09–1.43				
Industrial					4	234	0.85	0.74–0.96
Professional					9	263	1.31	1.16–1.47
All Leukemia	15	109	1.90	1.18–2.00				
Myeloid leukemia	6	61	1.9	1.31–2.76				
Industrial					4	122	0.9	0.75–1.07
Professional					10	106	1.39	1.15–1.68

Also available meta-analyses by Colins and Linker (2014) and Blair (2009) with similar results.

Zhang L et al., 2010 Environ Mol Mutagen. 2010 Apr;51(3):181-91

	Reference	Exposure Definition
Strong studies	Beane Freeman et al. 2009	Peak > 4ppm
	Beane Freeman et al. 2009	Peak > 4ppm prior to 1994
	Hauptmann et al. 2009	Ever Embalm
	Meyers et al. 2013	≥ 20 years since 1st exposure and ≥ 10 years exposed
Moderately strong studies	Coggon et al. 2014	Average > 2ppm
	Walrath and Fraumeni 1983	Exposed Profession
	Walrath and Fraumeni 1984	Exposed Profession
	Stroup et al. 1986	Exposed Profession
	Levine et al. 1984	Exposed Profession
	Bertazzi et al. 1989	Exposed Jobs
	Andjelkovich et al. 1995	Exposed Jobs
	Partanen et al. 1993	Exposed Jobs



NRC (2014) Review of the Formaldehyde Assessment in the National Toxicology Program 12th Report on Carcinogens https://doi.org/10.17226/18948

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US embalmers exposed to formaldehyde

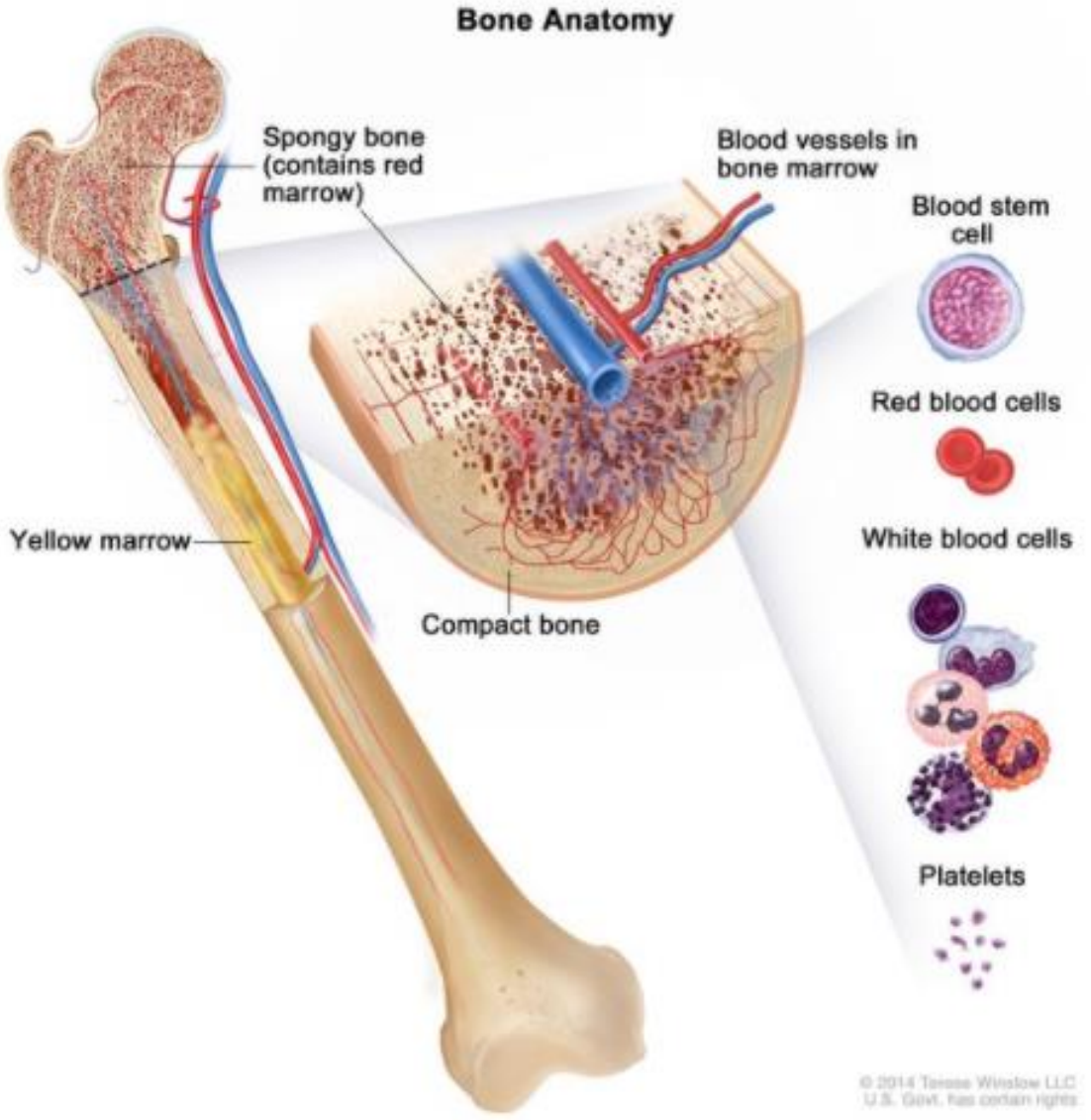
Characteristic	No. of control subjects	LHPM of nonlymphoid origin: No. of case subjects	LHPM of nonlymphoid origin: ORt (95% CI)	Myeloid leukemia: No. of case subjects	Myeloid leukemia: ORt (95% CI)	Acute myeloid leukemia: No. of case subjects	Acute myeloid leukemia: ORt (95% CI)
<500 embalmings	83	9	1.0 (Ref.)	5	1.0 (Ref.)	3	1.0 (Ref.)
>500 embalmings, questionnaire-based metrics							
Duration of working in jobs with embalming, y							
≤20	47	2	0.3 (0.1 to 1.7)	2	0.5 (0.1 to 2.9)	1	0.4 (0.04 to 4.9)
>20–34	67	16	2.0 (0.8 to 5.0)	13	3.2 (1.0 to 10.1)	8	2.9 (0.7 to 12.2)
>34	68	21	2.6 (1.0 to 6.4)	14	3.9 (1.2 to 12.5)	8	3.1 (0.7 to 13.7)
P for trend‡			.046 (.348)		.020 (.588)		.063 (.612)
[see original paper for complete table]							
TWA8 formaldehyde intensity, ppm							
≤0.10	56	9	1.3 (0.5 to 3.6)	8	2.4 (0.7 to 8.2)	3	1.4 (0.3 to 7.8)
>0.10 to .18	61	16	2.1 (0.8 to 5.3)	10	2.6 (0.8 to 8.7)	7	2.6 (0.6 to 11.4)
>0.18	65	14	1.9 (0.7 to 4.8)	11	2.6 (0.8 to 8.3)	7	2.6 (0.6 to 11.3)
P for trend‡			.256 (.951)		.396 (–.642)		.441 (–.672)
Peak formaldehyde exposure, ppm							
≤7.0	54	10	1.6 (0.6 to 4.5)	9	2.9 (0.9 to 9.8)	4	1.8 (0.4 to 9.3)
>7.0 to 9.3	66	12	1.4 (0.5 to 3.7)	9	2.0 (0.6 to 6.6)	5	2.1 (0.5 to 9.2)
>9.3	62	17	2.3 (0.9 to 5.6)	11	2.9 (0.9 to 9.5)	7	2.9 (0.7 to 12.5)
P for trend‡			.089 (–.944)		.036 (–.778)		.035 (.636)

‡ *P* trend (Wald test) among exposed only (ie, subjects who embalmed) in parentheses. Trend tests for LHPM of nonlymphoid origin and myeloid leukemia are the same as those presented in Table 3.

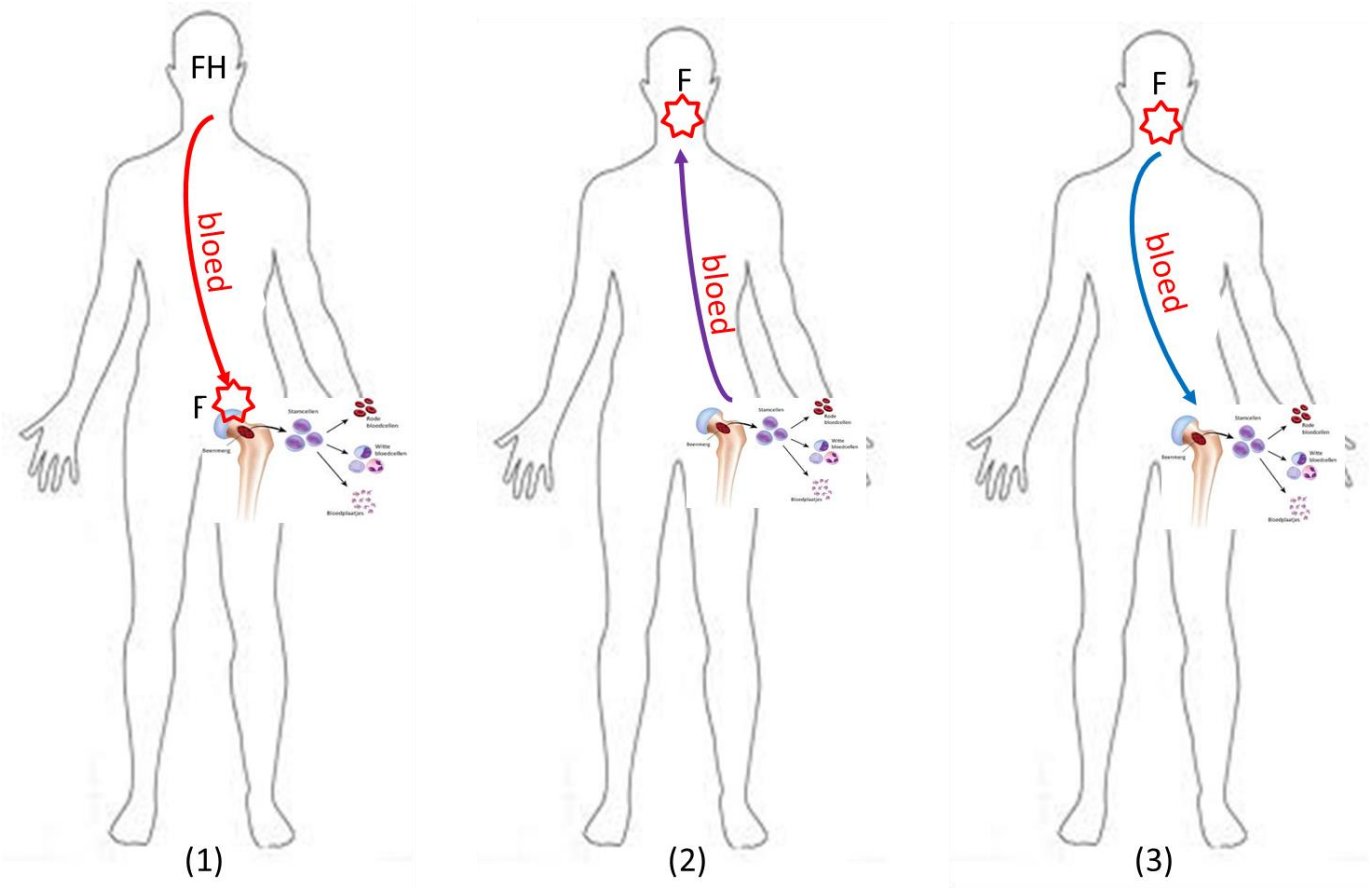
Modified from Hauptmann et al. (2009) J Natl Cancer Inst. 101(24):1696-708.

Bone marrow

Red marrow contains blood stem cells that can become red blood cells, white blood cells, or platelets.



Lymphohematopoietic cancer (LHC)



1. Formaldehyde hydrate reaches bone marrow via circulation and formaldehyde is reformed
2. Hematopoietic myeloid progenitor cells reach nose mucosa where they are transformed by formaldehyde
3. Nasal stem cells are damaged and then migrate to bone marrow

Zhang L et al., 2010 Environ Mol Mutagen. 2010 Apr;51(3):181-91.

Formaldehyde in drinking water study

FORMALDEHYDE: AN EXPERIMENTAL MULTIPOTENTIAL CARCINOGEN

MORANDO SOFFRITTI, CESARE MALTONI, FRANCESCA MAFFEI AND ROBERTA BIAGI

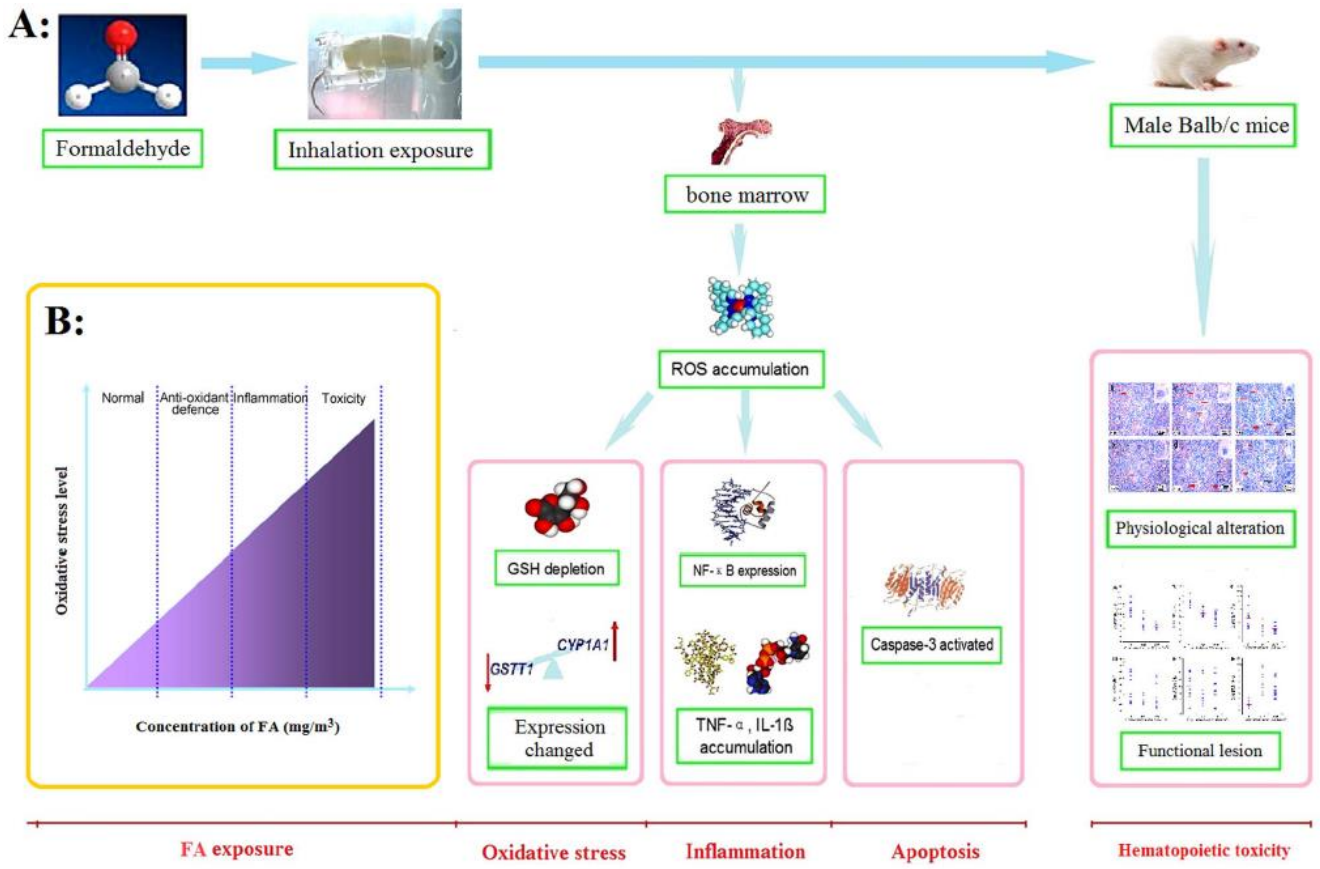
Institute of Oncology "F. Addarii", Bologna, Italy[1–4]

As far as the leukemogenic effects of formaldehyde on the Sprague-Dawley rats exposed by ingestion in the BT experiments are concerned, there is an interesting past observation of a bone marrow hyperplasia in Fischer-344 rats exposed by inhalation (Swemberg et al., 1980; Chemical Industry Institute of Toxicology Final Report, 1981). This change "was not considered a primary effect of formaldehyde exposure, but secondary to anoxia due to the presence of obstructive masses in the nasal passages" (Nelson et al., 1986). We think that this observation should now be reconsidered.

Toxicology and Industrial Health, Vol. 5, No. 5, 1989 699

In mouse in vivo

ROS-mediated inflammation in mice

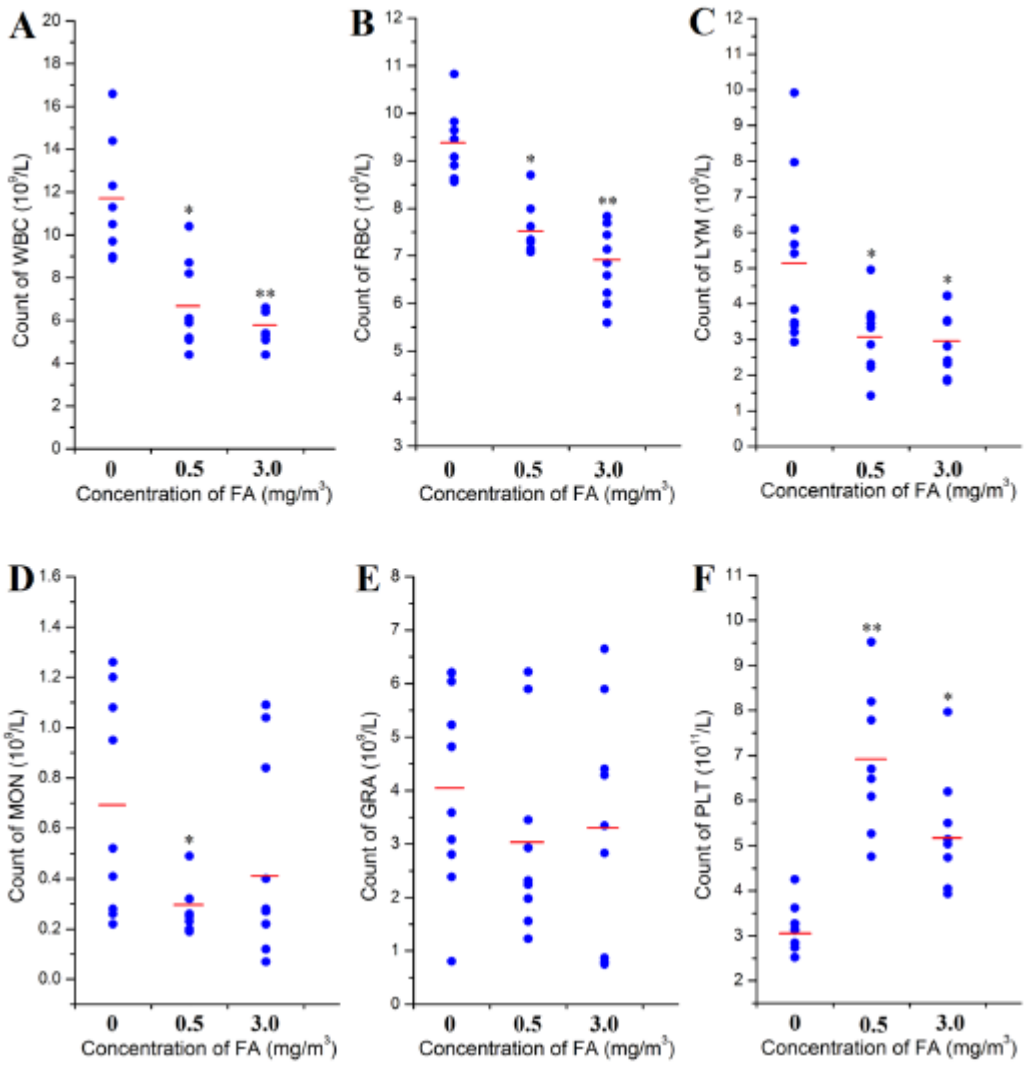


Zhang PLoS One. 2013 Sep 11;8(9):e74974.

In exposed mouse blood cells

Change in:

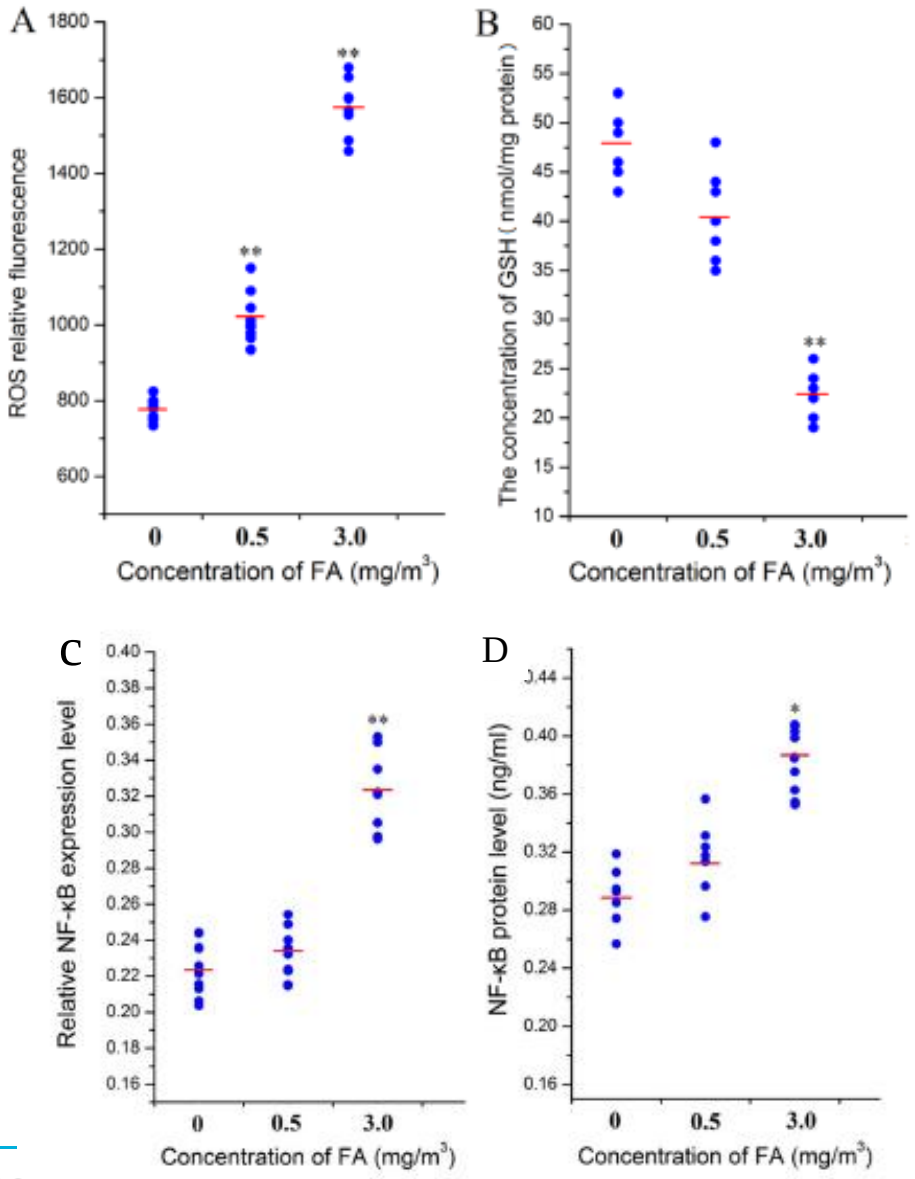
A. White blood cells
B. Red blood cells
C. Lymphocytes
D. Monocytes
E. Granulocytes
F. Platelets



Zhang PLoS One. 2013 Sep 11;8(9):e74974.

Biomarkers for oxidative stress and inflammation in mouse (in vivo)

A. A. Increase of reactive oxygen species (ROS)
B. Decrease of glutathione (GSH)
C. Increase of NFkB expression (inflammation)
D. Increase of NFkB proteins (inflammation)



Zhang PLoS One. 2013 Sep 11;8(9):e74974.

Fanconi anaemia

Normally the FA DNA-repair pathway ensures genome stability after exogenous formaldehyde exposure

Occurrence

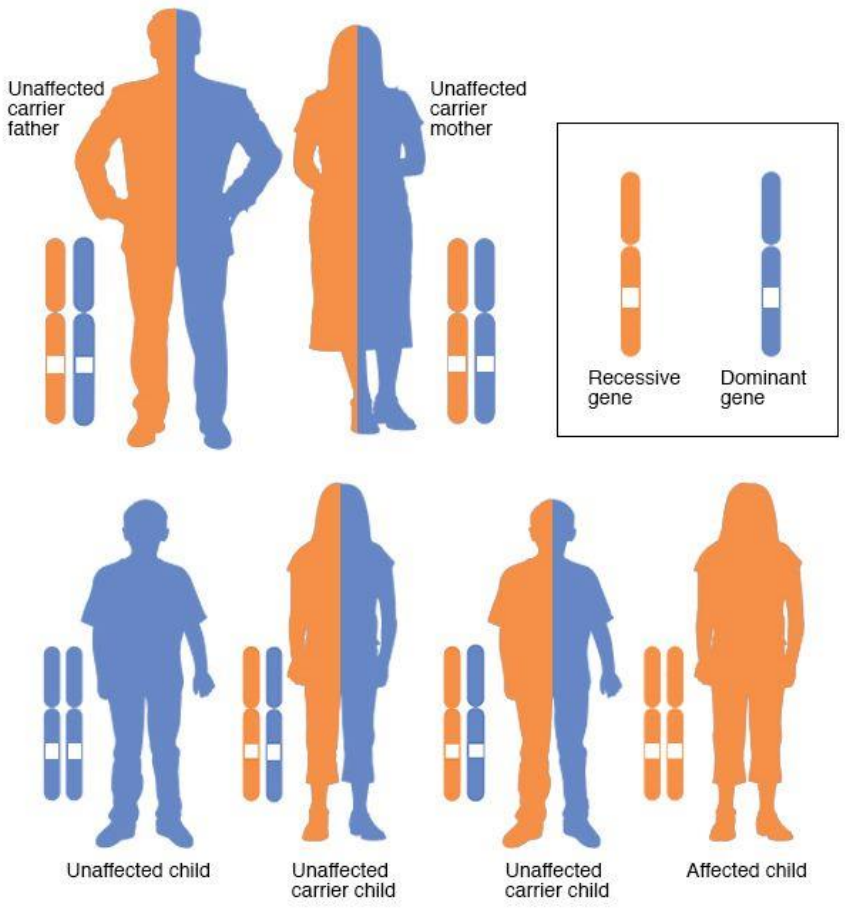
Incidence rate 1 in 160,000) and more frequent in Jews and Roma families

Consequences of a defect

- impaired response to DNA damage
- 90 % develop bone marrow failure by age of 40
- Majority develop acute myeloid leukemia (AML)

Treatment

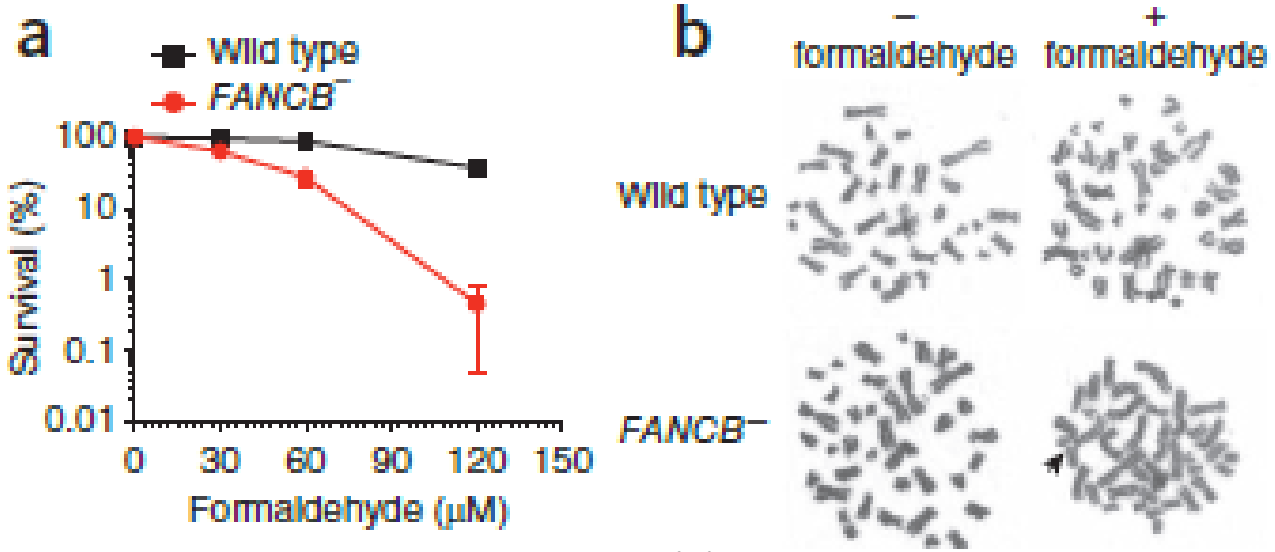
- Hematopoietic growth factors (50-75% response)
- Hematopoietic stem cell transplant
- Pre-implantation genetic diagnosis (PGD)



Autosomal recessive pattern of inheritance
https://www.pinterest.com/mayoclinic/

In vitro induced DNA-damage beyond repair in FANCB deficient human cells

Human B lymphocyte multiple lymphoma cell line (NALM-6)



(a) Human FANCB knockout cells are sensitive to exogenous formaldehyde when tested by MTS cell viability/proliferation assay.

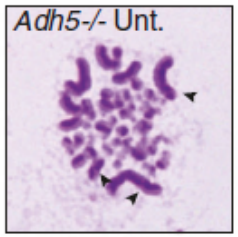
(b) Formaldehyde exposure in human FANCB− cells promotes chromosomal aberrations (left, arrowhead indicates radial structured chromosome; right, quantification of chromosomal aberrations, mean ± s.e.m., n = 2).

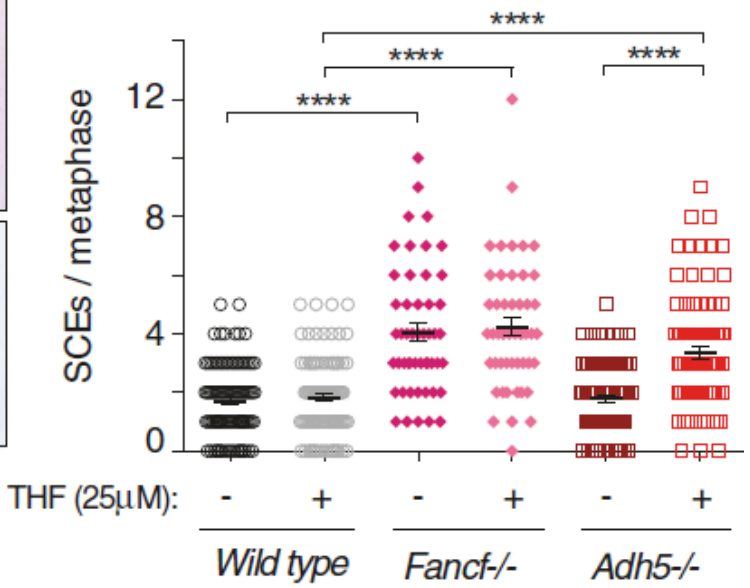
Rosado (2011) Nat Struct Mol Biol. 2011 Nov 13;18(12):1432-4. doi: 10.1038/nsmb.2173

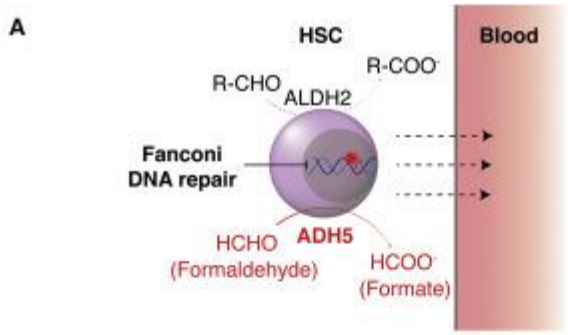
In vivo mouse model

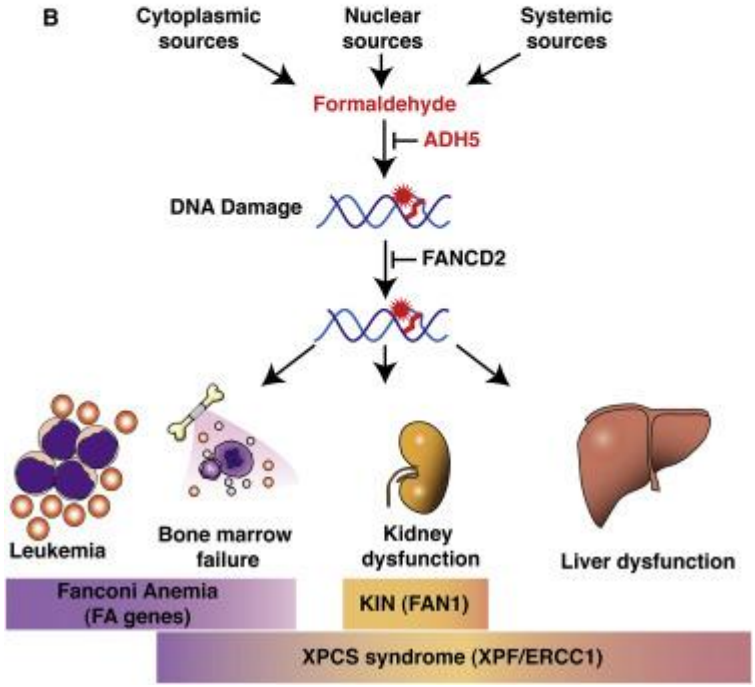
Study molecular mechanism systemic toxicity in wild type and

- Knock-out model for FANCD2$^{-/-}$
- Double knock-out model for ADH5$^{-/-}$ and FANCD2$^{-/-}$
- Knock-out model for ADH5$^{-/-}$









Pontel (2015) Mol Cell. 2015 Oct 1;60(1):177-88
García-Calderón et al. (2018) Cell Death Differ. 25(11):1967-1979

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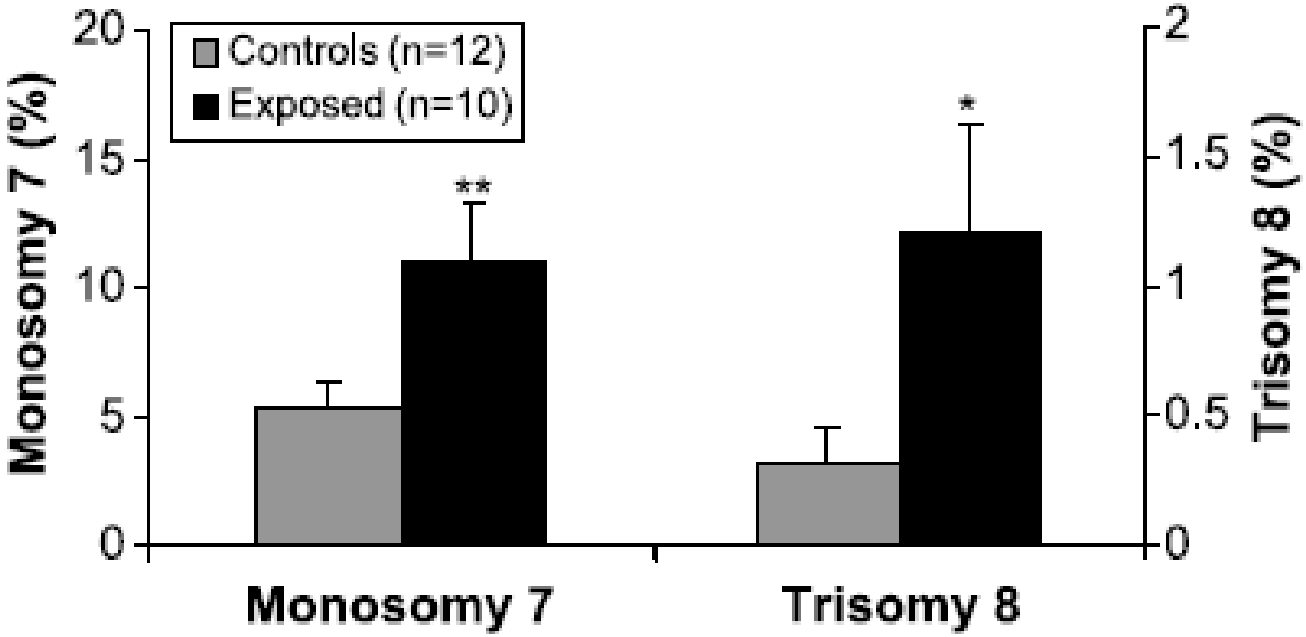
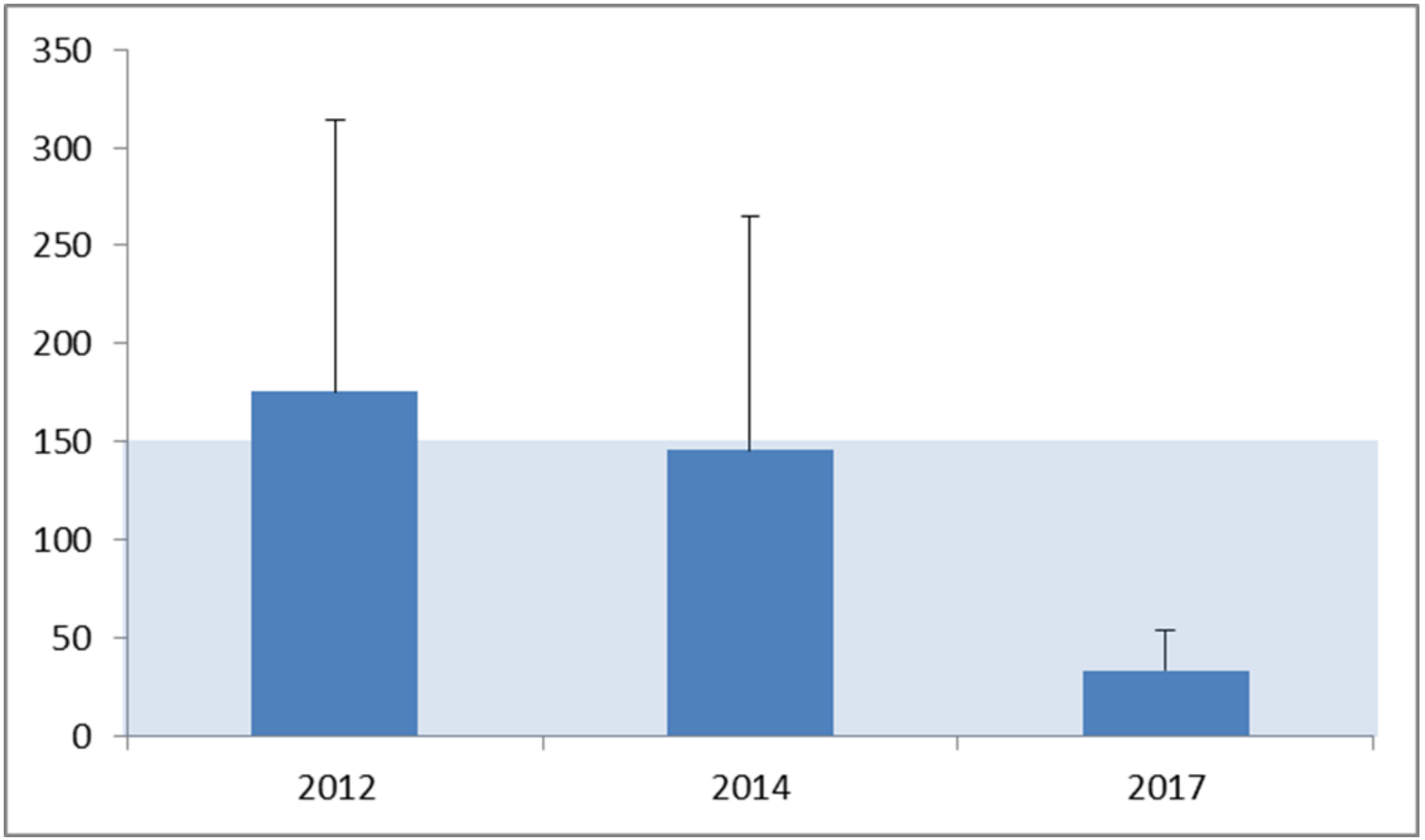
In workers in China



FISH test showed leukemia-specific chromosome changes in granulocyte-macrophage colony-forming units (CFU-GM), such as loss (monosomy) of chromosome 7 and gain (trisomy) of chromosome 8.
Controls: 0.026 ppm; exposed: 2.14 ppm; *, $P < 0.05$; **, $P < 0.01$

Formaldehyde concentrations in breathing zone (8-h) (occupational exposure limit is 150 µg/m^3)



Source: Scheepers (2018) Changes in Work Practices for Safe Use of Formaldehyde in a University-Based Anatomy Teaching and Research Facility. Int J Environ Res Public Health. 2018 Sep 19;15(9):2049.

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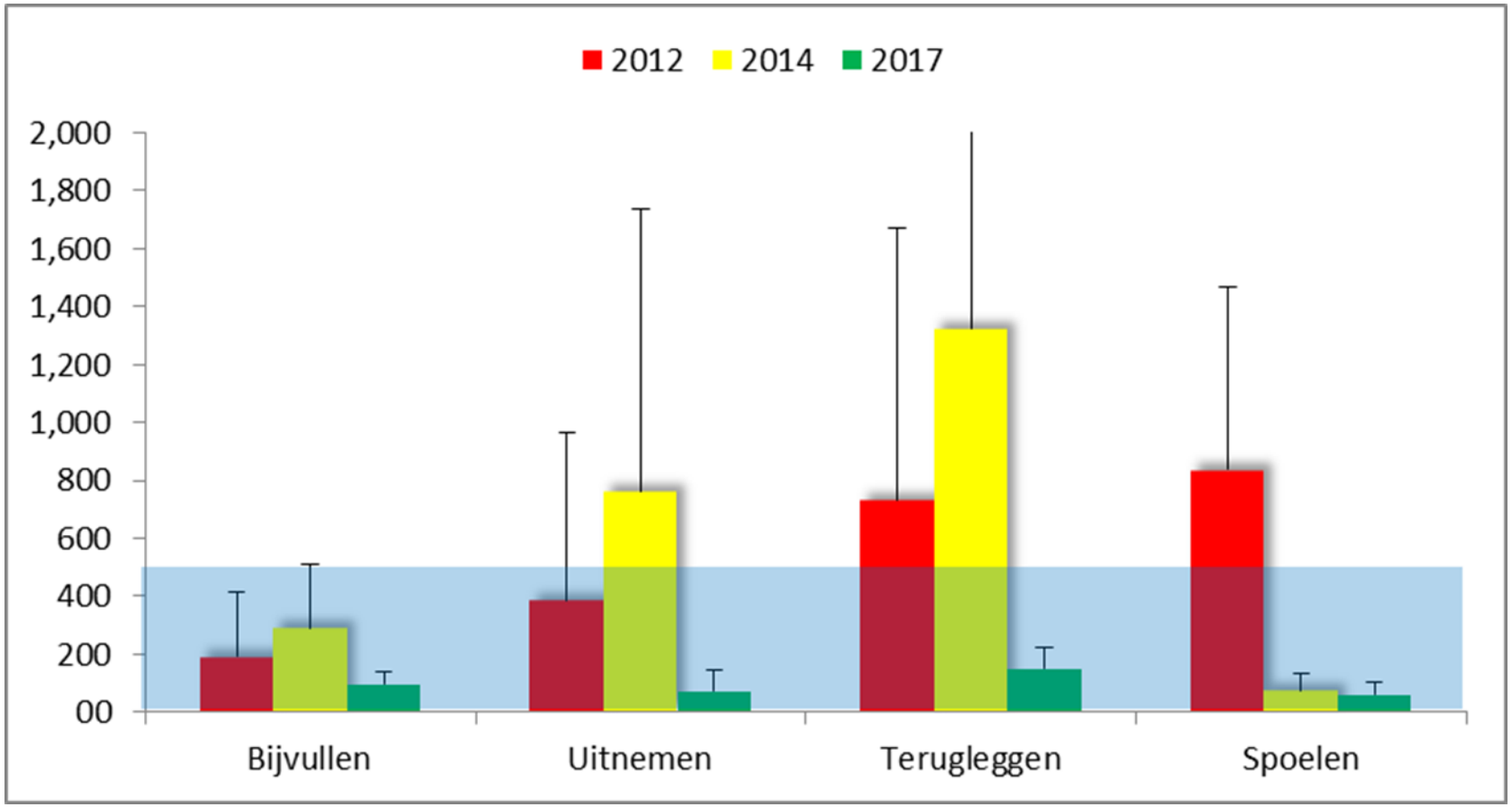
Formaldehyde concentrations in breathing zone (15 min) (occupational exposure limit 500 µg/m³)



Source: Scheepers (2018) Changes in Work Practices for Safe Use of Formaldehyde in a University-Based Anatomy Teaching and Research Facility. Int J Environ Res Public Health. 2018 Sep 19;15(9):2049.

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Take ‘where-ever-you-go’ message

1. There is sufficient evidence for **local tumors** in the nose and nasal sinuses.
2. There **limited probabilistic evidence** for inhaled formaldehyde to be leukemogenic. However, animal *in vivo* bioassays have so far not been able to confirm DNA protein cross links and adducts in bone marrow derived from exogenous formaldehyde.
3. Human evidence in systematic review shows overall higher risk in **professional user** than industrial use (why?)
4. With a short-term exposure limit the Health Council of the Netherlands **preluded on adversity of peak exposures** in the nasal respiratory epithelium
5. For the moment (and perhaps also for the future) it is warranted to **evaluate task-based ‘peak exposures’** using the 15-min OEL in addition to 8-h TWA.

Why is understanding causation so important in philosophy and the sciences? Should causation be defined in terms of probability? Whilst causation plays a major role in theories and concepts of medicine, little attempt has been made to connect causation and probability with medicine itself. Causality, Probability, and Medicine is one of the first books to apply philosophical reasoning about causality to important topics and debates in medicine.

https://donaldgillies.wordpress.com/

CAUSALITY, PROBABILITY, AND MEDICINE

DONALD GILLIES

August 2018

ROUTLEDGE